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(54) Title: BACTERICIDAL, ANTI-APOPTOTIC, PRO-INFLAMMATORY AND ANTI-INFLAMMATORY PEPTIDES OF HEPARIN-BINDING PROTEIN (HBP)

(57) Abstract: The present invention relates to providing new peptide fragments derived from the sequence of heparin-binding protein (HBP) and/or human neutrophil elastase and using said fragments for the manufacture of a medicament for the treatment of Gram positive and/or Gram negative infections. Thus, the peptides of the inventions can be used for treatment of pneumonia and meningitis. The peptides of the invention may also be advantageously used for the treatment of any pathological condition demanding modulating of inflammatory response and/or a condition involving sepsis and/or, disseminated intravascular coagulation. Among other pathological conditions, which may be regarded for the treatment with the peptides of the invention, are conditions involving cell apoptosis.

**Bactericidal, anti-apoptotic, pro-inflammatory and anti-inflammatory peptides
of heparin-binding protein (HBP)**

5 Technical field of the invention

The present invention relates to providing peptides derived from the sequence of heparin-binding protein (HBP) and/or human neutrophil elastase and using said peptides for the manufacture of a medicament for the treatment of Gram positive
10 and/or Gram negative infections, sepsis, disseminated intravascular coagulation, modulation of inflammatory response, and/or prevention of cell apoptosis.

Background of the invention

15 A local infection or injury in any tissue rapidly attracts white blood cells into the affected region as part of the inflammatory response, which helps fight the infection or heal the wound. The inflammatory response is complex and is mediated by a variety of signalling molecules produced locally by different types of cells. Some of these molecules act on nearby capillaries, causing the endothelial cells to adhere
20 less tightly to one another but making their surfaces adhesive to passing white blood cells. Other molecules act as chemoattractants for specific types of blood cells, such as monocytes, causing these cells to become polarised and crawl toward the source of the attractant.

25 White blood cells, specifically polymorphonuclear leukocytes (PMNs), produce a large variety of peptides involved in the inflammatory response. Among these peptides is the heparin-binding protein (HBP), which was first isolated from azurophile granules of human PMNs. A highly homologous peptide was also isolated from PMNs of porcine origin and has been named porcine heparin-binding
30 protein (pHBP) (Flodgaard et al., 1991, Eur. J. Biochem. 197: 535-547; Pohl et al., 1990, FEBS Lett. 272: 200 ff.) HBP has otherwise been termed CAP37 (WO 91/00907, US 5,458,874 and 5,484,885) and azurocidin (Wilde et al. 1990, J. Biol. Chem. 265:2038-41).

35 Sequence analysis of HBP has revealed that the protein bears many similarities to serine proteases, which are important in inflammatory processes, e. g. neutrophil

elastase (47% homology) or protease 3 (43% homology), however HBP lacks protease activity due to mutations of two of three amino acids in the highly conserved catalytic triad. The structure of HBP appears from WO 89/08666 and Flodgaard et al., 1991 (Eur. J. Biochem. 197: 535-547).

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HBP was originally studied because of its antibiotic and lipopolysaccharide binding properties (Gabay et al., 1989, Proc. Natl. Acad. Sci. U.S.A. 86:5610-5614 and Pereira et al., 1993, Proc. Natl. Acad. Sci. USA 90: 4733-7). However, a number of experimental evidence now supports the concept that HBP is a multifunctional protein, and, in addition to its bactericidal role, is involved during the progression of inflammation due to its effect on the recruitment and activation of monocytes (Pereira et al., 1990, J. Clin. Invest. 85:1468-1476, and Rasmussen et al., 1996, FEBS Lett. 390:109-112), recruitment of T cells (Chertov et al., 1996, J. Biol. Chem. 271:2935-2940), as well as on the induced contraction of endothelial cells and fibroblasts (Ostergaard and Flodgaard, 1992, J. Leuk. Biol. 51:316-323). Ostergaard and Flodgaard (op. cit.) also disclose increased survival of monocytes treated with HBP. Furthermore, in animal models of fecal peritonitis, HBP treatment has been shown to rescue mice from an otherwise lethal injury (Mercer-Jones et al., 1996, In: Surgical Forum, pp. 105-108; Wickel et al., 1997, In: 4th International Congress on the Immune Consequences of Trauma, Shock and Sepsis, Munich, Germany, pp. 413-416).

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Using synthetic peptides derived from the sequence of human HBP in laboratory and preclinical research some functions of the protein has been structurally localised within the molecule of HBP. Thus, it has been shown that, for example, a high Gram negative bactericidal activity of human HBP is most probably associated with residues 20-44 of the human HBP amino acid sequence (Pereira et al., 1993, Proc. Natl. Acad. Sci. USA 90: 4733-7 and US 6,107,460). The amino acid residues 95-122 of the human HBP sequence have been associated with a capacity of the protein to stimulate protein kinase C in vascular endothelial cells (Pereira et al., 1996, J. Leukoc. Biol. 60:415-22).

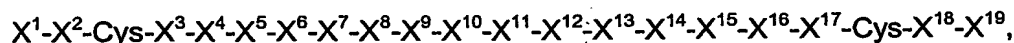
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It would be advantageous to produce new peptides derived from the sequence of human HBP, porcine HBP, or analogues of these sequences, such as, for example, neutrophil elastase, to use for the manufacture of new bactericidal, anti-apoptotic

medicaments and medicaments for modulation of an inflammatory response, especially the inflammatory response to bacterial infection.

Summary of the invention

Thus, in one embodiment the present invention relates to providing peptides having a peptide having a sequence of at most 44 amino acid residues comprising a motif of the formula



wherein

the side chains of the two Cys residues are connected via a disulfide bond,

wherein

X can be an amino acid sequence or a single amino acid residue selected either from Group 1 consisting of Ala, Gly, and Ser,

Group 2 consisting of Arg and Lys,

Group 3 consisting of His, Ile, Leu, Met, Phe, Pro, Thr, Val, Trp, and Tyr,

Group 4 consisting of Asn and Gln, or

Group 5 consisting of Ala, Asn, Arg, Gln, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, Val,

wherein

X¹ can be represented by a sequence consisting of 2-5 amino acid residues or an amino acid residue selected from Group 2;

X² is selected from Group 5 or Group 3;

X³, X¹⁵ and X⁴ are selected from Group 1;

X⁵ is Thr or selected from from Group 1;

X⁶, X¹¹, X¹², X¹³ and X⁷ are selected from Group 3;

X⁸ and X¹⁷ are selected from Group 1, 3 or 4;

X⁹ is selected from from Group 5, 1 or 3;

X¹⁰ is selected from from Group 2, 3 or 4;

X¹⁴ is Ser or selected from from Group 3;

X¹⁶ and X¹⁸ is selected from Group 1 or 3

X¹⁹ can be represented by a sequence consisting of 2-5 amino acid residues or a

single amino acid residue selected from Group 5, 2, or 4,

with the proviso, that when X¹ includes Pro, then X¹⁹ is Gln.

The invention concerns providing peptides derived from the sequence of human HBP (hHBP) and/or porcine HBP (pHBP) and/or human neutrophil elastase capable of
5 proinflammatory or anti-inflammatory activity, bactericidal and/or monocyte attractive activity, and/or capable of preventing cell apoptosis.

Further, the present invention discloses a recombinant process for the production of the above peptides, and the use of the peptides of the invention for the manufacture
10 of a medicament for prevention or treatment of Gram negative and/or Gram positive bacterial infections, sepsis, severe sepsis, septic shock, disseminated and/or intravascular coagulation, stimulation or inhibition of the inflammatory response, or cell apoptosis.

15 Figures

Figure 1 depicts IL-6 secretion induced by HBP peptides in the absence of bacterial components.

20 Figure 2 shows the effect of HBP 20-44 peptides on LPS induced IL-6 secretion

Figure 3 shows the effect of HBP 20-44 peptides on LPS induced IL-6 secretion in the presence of PGN.

25 Figure 4 shows the effect of HBP 20-44 peptides on LPS induced IL-6 secretion in the presence of PCW.

30 Figure 5 shows the effect of N-Ac, C-amido hHBP 20-44 on PGN induced IL-6 secretion.

Figure 6 shows the effect of R34Q pHBP 20-44 on PGN induced IL-6 secretion.

35 Figure 7 shows the effect of different substitutions in the sequence of hHBP and p HBP on production of IL-6 induced by LPS.

Figure 8 shows the effect of different substitutions in the sequence of hHBP and p HBP on production of IL-6 induced by PGN.

5 Table 1 shows the potential applications for mono-functional peptides of the invention.

Detailed description of the invention

10 Inflammation

The present invention relates to providing peptides and using said peptides for the manufacture of a medicament for modulation of the inflammatory response.

15 Inflammation is a defence reaction caused by tissue damage due to a mechanical injury or bacterial, virus or other organism infection. The inflammatory response involves three major stages: first, dilation of capillaries to increase blood flow; second, microvascular structural changes and escape of plasma proteins from the blood-stream; and third, leukocyte transmigration through endothelium and accumulation
20 at the site of injury and infection. The inflammatory response begins with a release of inflammatory mediators. Inflammatory mediators are soluble, diffusible molecules that act locally at the site of tissue damage and infection, and at more distant sites, influencing consequent events of the inflammatory response. Inflammatory mediators can be exogenous, e. g. bacterial products or toxins, or endogenous, which are
25 produced within the immune system itself, as well as injured tissue cells, lymphocytes, mast cells and blood proteins.

In one aspect the present invention relates to the inflammatory response to bacterial infection.

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By "bacterial infection" in the present context is meant the invasion of normally sterile host tissue by bacteria. Bacterial infection of the invention may be due to invasion of either Gram negative or Gram positive bacteria, or a combination thereof or other infectious agents including fungi and virus. In one embodiment the present invention
35 relates to the inflammatory response due invasion of Gram negative bacteria se-

lected from the group comprising Acetobacteriaceae, Alcaligenaceae, Bacteroidaceae, Chromatiaceae, Enterobacteriaceae, Legionellaceae, Neisseriaceae, Nitrobacteriaceae, Pseudomonadaceae, Rhizobiaceae, Rickettsiaceae, Spirochaetaceae, Vibrionaceae, Brucella, Chromobacterium

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In another embodiment the invention relates to the inflammatory response due to invasion by Gram positive bacteria selected from the group comprising Bacillaceae, Micrococcaceae (for example *Staphylococcus aureus*), Mycobacteriaceae (for example *Staphylococcus pneumoniae*), Peptococcaceae.

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In an additional another embodiment the invention relates to the inflammatory response associated with sepsis, severe sepsis and/or septic shock.

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By "sepsis" in the present context is meant the systematic inflammatory response to bacterial infection, characterised by one or more of the following conditions as a result of infection: temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, heart rate >90 beats/min, respiratory rate >20 breaths/min or $\text{PaCO}_2 <32$ torr (<4.3 kPa), and WBC $>12\,000$ cells/ mm^3 or <4000 cells/ mm^3 or 10% immature (band) forms.

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By "severe sepsis" in the present context is meant sepsis associated with organ dysfunction, hypoperfusion, or hypotension, hypoperfusion and hypotension abnormalities may include, but are not limited to, lactic acidosis (acidic condition in blood), oliguria (meaning reduction in urine production), or acute alteration in mental status.

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By "septic shock" in the present context is meant sepsis with hypotension despite adequate fluid resuscitation, along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or acute alteration in mental status.

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In yet another embodiment the invention relates to the inflammatory response associated with disseminated intravascular coagulation (DIC).

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By "DIC" in the present context is meant a pathophysiologic condition involving a continuum of events that occur in the coagulation pathway in association with a variety of well-defined clinical situations, including sepsis, major trauma, and abruptio placenta, and with laboratory evidence of the following: procoagulant activation, fi-

brinolytic activation, inhibitor consumption and biochemical evidence of end-organ damage or failure.

Proinflammatory peptides

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It is an objective of the present invention to provide new peptides, which are capable to serve as additional mediators of the inflammatory response, the so-called pro-inflammatory peptides are particularly useful but not limited to patients selected from groups of immune-suppressed patients, cancer patients, patients with autoimmune diseases and patients undergoing major surgery.

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In the present context by the term " pro-inflammatory peptide" is meant an artificial peptide compound which is capable of

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i) Stimulating, either alone or in synergistic action with bacterial products including, but not limited to LPS (Lipopolysaccharide), PGN (peptidoglycan), LTA (Lipotechoic acid), MDP (muramyl dipeptide) and PCW (purified cell wall from bacteria), the gene expression in the immune cells, preferably monocytes/macrophages, leading to secretion of endogenous inflammatory mediators including receptors for inflammatory mediators and transcription factors involved in the signal transduction of the inflammatory mediators, said mediators being preferably selected from the group comprising cytokines, selected from the group TNF α , IL-1, IL-6, G-CSF, GM-CSF, M-CSF. Chemokines selected from the group comprising IL-8, MCP-1, receptors selected from the group Tissue factor and IL-2R α . and/or

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- ii) activating the production of bradykinin by the phase contact system, and/or;
- iii) serving as an attractant for monocytes, and/or
- iv) increasing the life-time of monocytes, neutrophils and other immune cells serving as an inhibitor of apoptosis, and/or
- v) activating vascular endothelial cells to express the adhesion molecules, said adhesion molecules being preferably selected from the group comprising PECAM, ICAM-1, E-selectins, VCAM-1, and/or
- vi) activate the contact phase system to produce bradykinin leading to an increased vascular permeability, and/or
- vii) increase the phagocytic potential of monocytes/macrophages, and/or
- viii) upregulate class-II MHC.

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In one embodiment the pro-inflammatory peptide of the invention is a peptide

- i) derived from any of the sequences set forth in SEQ ID NO: 1, SEQ ID NO:588, or SEQ ID NO: 589,
- 5 ii) comprising one or more of the sequences set forth in SEQ ID NO: 2-587,
- iii) capable of at least one of the above activities (i-viii) of an pro-inflammatory compound, more preferable at least two of the above activities, even more preferable at least three of the above activities, even more preferable at least four of the above activities, even more preferable at least five of the above activities, even more preferable at least six of the above activities, even more preferable at least seven of the above activities, and most preferably eight of the above activities.

In the present context the term "synergistic action" refers to the situation where the combined action of a bacterial product and a peptide of the present invention is a stronger pro-inflammatory stimulant than the pro-inflammatory stimulant a bacterial product or the present peptide, respectively would be on their own.

In another embodiment the invention provides a pro-inflammatory peptide capable of stimulating either alone or in synergistic action with bacterial products including, but not limited to LPS (Lipopolysaccharide), PGN (peptidoglycan), LTA (Lipotechoic acid), MDP (muramyl dipeptide) and PCW (purified cell wall from bacteria) the secretion of cytokine IL-6 from monocytes, comprising two or more sequences set forth in SEQ ID NOS: 15-36, wherein said sequences constitute a contiguous sequence derived from the sequence of hHBP set forth in SEQ ID NO:1. Further, the pro-inflammatory peptide may be used for the manufacture of a medicament for the treatment of individuals having suppressed immune system, cancer, auto-immune diseases and/or trauma.

In a preferred embodiment the invention concerns an pro-inflammatory peptide, wherein said peptide has the sequence NQGRHF CGGALIHARFVMTAASCFQ (SEQ ID NO: 594). Even more preferred the peptide, wherein the sequence identified in SEQ ID NO: 594 has the N-terminal and C-terminal modified, as for example the N-terminal amino group being amidated and the C-terminal carboxy group being acetylated.

Anti-inflammatory peptides

It is another important objective of the invention to provide new anti-inflammatory peptide, which are capable of serving as inhibitors of the sustained inflammatory response.

The continuous presence of inflammatory mediators, such as for example TNF alpha in the body in response to sustained presence of bacterial products or even live bacteria locally during days or weeks following trauma and/or infection promotes the reactions to inflammation, such as, for example, heat, swelling, and pain. The sustained inflammatory response has been proven to be very harmful to the body. If the bacterial products or live bacteria become spread universally in the body from their local focus the inflammatory reaction becomes overwhelming and out of control and leads to sepsis which eventually progress further to severe sepsis and septic shock. Anti-inflammatory peptides may be used to block or suppress the overwhelming sustained inflammatory response represented by a massive and harmful cytokine cascade in the blood and vital organs such as lung, liver intestine, brain and kidneys.

In the present context by the term "anti-inflammatory compound" is meant a compound which is capable of

- i) decreasing or inhibiting the gene expression in the immune cells, preferably monocytes/macrophages in response to bacterial products, live bacteria or trauma to produce endogenous inflammatory mediators including receptors for inflammatory mediators and transcription factors involved in the signal transduction of the inflammatory mediators, said mediators being preferably selected from the group comprising cytokines, selected from the group TNFalpha IL-1, IL-6, G-CSF, GM-CSF, M-CSF. Chemokines selected from the group comprising IL-8, MCP-1, receptors selected from the group Tissue factor and IL-2Ralpha. and/or
- ii) decrease or inhibit the production bradykinin by the phase contact system, and/or;
- iii) decrease or inhibit the attractant potential for monocytes, and/or
- iv) decrease or inhibit the life-time of monocytes, neutrophils and other immune cells serving as an inducer of apoptosis, and/or

- v) decrease or inhibit vascular endothelial cells to express the adhesion molecules, said adhesion molecules being preferably selected from the group comprising PECAM, ICAM-1, E-selectins, VCAM-1 and/or
- vi) decrease or inhibit activation of the contact phase system to produce bradykinin leading to increased vascular permeability, and/or
- vii) stimulate the synthesis of an anti-inflammatory mediator selected from the group of IL-10 and IL-12, and/or
- viii) removing endotoxin from septic patients, and/or

10 In one embodiment the anti-inflammatory peptide compound of the invention is a peptide

- i) derived from any of the sequences set forth in SEQ ID NO: 1, SEQ ID NO: 588, or SEQ ID NO: 589,
- ii) comprising one or more of the sequences set forth in SEQ ID NO: 2-587,
- 15 iii) capable of at least one of the above activities of an anti-inflammatory compound, more preferable at least two of the above activities, even more preferable at least three of the above activities, even more preferable at least four of the above activities, even more preferable at least five of the above activities, even more preferable at least six of the above activities, even more preferable at least seven of the above activities, even more preferable at least eight of the above activities, and most preferably nine of the above activities.

25 In another embodiment the invention provides an anti-inflammatory peptide capable of inhibiting the secretion of cytokine IL-6 from monocytes in response to bacterial products including, but not limited to, LPS (Lipopolysaccharide), PGN (peptidoglycan), LTA (Lipotechoic acid), MDP (muramyl dipeptide) and PCW (purified cell wall from bacteria), comprising two or more sequences set forth in SEQ ID NOS: 233-253, wherein said sequences constitute a contiguous sequence
30 derived from the sequence of pHBP set forth in SEQ ID NO: 588.

In a preferred embodiment of the invention an inflammatory peptide has the sequence KQGRPFCAGALVHPRFVLTAASCFR (SEQ ID NO: 593). Even more preferred the peptide, wherein the sequence identified in SEQ ID NO: 593 has the

N-terminal and C-terminal modified, as for example the N-terminal amino group being amidated and the C-terminal carboxy group being acetylated.

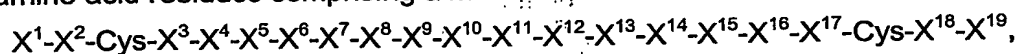
Peptides

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It is an objective of the present invention to provide one or more peptides for the manufacture of a medicament for prevention and/or treatment of Gram positive and/or Gram negative infections, sepsis, severe sepsis, septic shock and/or disseminated intravascular coagulation, and/or for modulation of inflammatory response, and/or prevention of cell apoptosis.

10

In one embodiment the invention concerns a peptide having a sequence of at most 44 amino acid residues comprising a motif of the formula



15

wherein

the side chains of the two Cys residues are connected via a disulfide bond,

wherein

X can be an amino acid sequence or a single amino acid residue selected either from Group 1 consisting of Ala, Gly, and Ser,

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Group 2 consisting of Arg and Lys,

Group 3 consisting of His, Ile, Leu, Met, Phe, Pro, Thr, Val, Trp, and Tyr,

Group 4 consisting of Asn and Gln, or

Group 5 consisting of Ala, Asn, Arg, Gln, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, Val,

25

wherein

X¹ can be represented by a sequence consisting of 2-5 amino acid residues or an amino acid residue selected from Group 2;

X² is selected from Group 5 or Group 3;

X³, X¹⁵ and X⁴ are selected from Group 1;

30

X⁵ is Thr or selected from from Group 1;

X⁶, X¹¹, X¹², X¹³ and X⁷ are selected from Group 3;

X⁸ and X¹⁷ are selected from Group 1, 3 or 4;

X⁹ is selected from from Group 5, 1 or 3;

X¹⁰ is selected from from Group 2, 3 or 4;

35

X¹⁴ is Ser or selected from from Group 3;

X¹⁶ and X¹⁸ is selected from Group 1 or 3

X¹⁹ can be represented by a sequence consisting of 2-5 amino acid residues or a single amino acid residue selected from Group 5, 2, or 4, with the proviso, that when X¹ includes Pro, then X¹⁹ is Gln.

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In a preferred embodiment X¹ in sequence of the peptide of the invention is represented by an amino acid sequence selected from SEQ ID NOS: 607-612. In another preferred embodiment X¹ is Arg. Another preferred embodiment for the sequence of the peptide is Phe in position X². It is also preferred Ala or Gly as the X³ residue. The peptide preferably has Gly as the X⁴ residue. The X⁵ residue is preferably represented by Ala, and X⁶ by Leu. The X⁷ may preferably be selected from the group containing Ile, Leu, Met or Val. The peptide according to another preferred embodiment has X⁸ represented by His or Val. The position X⁹ in the sequence of the peptide may preferably be occupied by a residue selected from Ala, Phe or Pro. X¹⁰ is preferably represented by Arg, and X¹¹ is Phe or Pro. The position X¹² is preferably occupied by His or Val, and X¹³ is preferably selected from the group consisting Ile, Leu, Met or Val. The peptide has preferably Thr in position X¹⁴, Ala in position X¹⁵ and X¹⁶, and X¹⁷ is preferably Ser. The X¹⁸ residue is preferably represented by Phe. X¹⁹ in one preferred embodiment is represented by a sequence identified as SEQ ID NO: 613, and in another preferred embodiment is represented by Arg or Gln.

Another preferred embodiment of a peptide having the sequence comprising the above motif is that N-terminal and/or C-terminal of said peptide may be modified. Thus, the C-terminal carboxy group in a more preferred embodiment is amidated, and the N-terminal in another more preferred embodiment is acetylated.

Furthermore, the invention in the other preferred embodiments concerns particular amino acid sequences comprising the motif disclosed above. Thus, the peptide according to the present invention preferably has a sequence selected from

KQGRPFCAGALVHPRFVLTAASCFR (SEQ ID NO: 593),
NQGRHFCGGALIHARFVMTAASCFQ (SEQ ID NO: 594),
KQGRHFCGGALIHARFVMTAASCFR (SEQ ID NO: 595),
KQGRPFCGGALIHARFVMTAASCFR (SEQ ID NO: 596),
KQGRHFCGGALIHPRFVMTAASCFR (SEQ ID NO: 597),

KQGRPFCGGALIHPRFVMTAASCFR (SEQ ID NO: 598),
RFCSAATLVFRPHVLAGACFPRGQK (SEQ ID NO: 599),
NQGRPFCAGALVHPRFVLTAASCFR (SEQ ID NO: 600),
KQGRPFCAGALVHPRFVLTAASCFQ (SEQ ID NO: 601),
5 NQGRPFCAGALVHPRFVLTAASCFQ (SEQ ID NO: 602),
KQGRPFCAGALVHPQFVLTAASCFR (SEQ ID NO: 603),
LRGGHFCGATLIAPNFVMSAAHCVA (SEQ ID NO: 604),
RRGGHFCGATLIARNFVMSAVHCVN (SEQ ID NO: 605) and
RSREYRCGGTLVSQRYILTAASCAA (SEQ ID NO: 606).

10 The sequences identified in SEQ ID NO: 593 and 594 according to the invention are preferably modified in the N- and C-terminus as described above.

15 All peptides of at most 44 amino acids length comprising the motif as above are in the scope of the present invention. However, the invention preferably concerns peptides wherein the positions X^{15} - X^{16} - X^{17} in the motif are Ala-Ala-Ser correspondingly, in positions X^1 to X^{14} and X^{18} to X^{19} may be any amino acid residues connected in a contiguous polypeptide chain. The preferred embodiments for the positions are as described above. Moreover, it is further preferred, if the
20 peptide comprises one or more amino acid sequences are selected from SEQ ID NOS: 12-39. Another preferred embodiment if the sequence comprises one or more amino acid sequences are selected from SEQ ID NOS: 233-253. It is still another preferred embodiment if the peptide comprises one or more amino acid sequences are selected from SEQ ID NOS: 233-253 and SEQ ID NO: 34. In yet preferred
25 embodiment the peptide comprises one or more amino acid sequences selected from SEQ ID NOS: 233-253 and SEQ ID NO: 21. Still yet preferred embodiment is a peptide comprising one or more amino acid sequences are selected from SEQ ID NOS: 233-253 and SEQ ID NO: 21 and SEQ ID NO: 34. Also preferred a peptide comprising one or more amino acid sequences are selected from SEQ ID NOS:
30 395-421.

The sequences of the peptide may be derived from any longer polypeptide sequence of natural or artificial origin. However the invention concerns some preferred embodiments for such the sequence. In a first preferred embodiment the
35 invention concerns one or more amino acid sequences which are derived from the

sequence of human heparin-binding protein (hHBP) set forth in SEQ ID NO: 1. In another preferred embodiment the invention concerns one or more amino acid sequences derived from the sequence of porcine heparin-binding protein (pHBP) set forth in SEQ ID NO: 588. In still another, preferred embodiment the invention
5 concerns one or more amino acid sequences derived from the sequence of human neutrophil elastase set forth in SEQ ID NO: 589.

Additionally, a preferred peptide comprising the above motive according to the invention comprises one or more amino acid sequences set forth in SEQ ID NOS: 2-
10 587.

A peptide as described above according to the invention is capable of inhibiting the secretion of cytokine IL-6 from monocytes.

15 It is another objective of the present invention to produce peptides as small as possible, yet exhibiting the desired effect(s).

In one embodiment, the invention relates to providing a peptide consisting of at most 8 amino acids comprising one or more of the amino acid sequences set forth in SEQ
20 ID NOS: 2-587.

In another embodiment, the invention relates to providing a peptide consisting of at most 12 amino acids comprising one or more of the amino acid sequences set forth in SEQ ID NOS: 2-14, 22-36, 46-107, 115-185 and 195-587.
25

In still another embodiment, the invention relates to providing a peptide consisting of at most 16 amino acids comprising one or more of the amino acid sequences set forth in SEQ ID NOS: 2-14, 46-107, 115-185 and 195-587.

30 In yet another embodiment, the invention relates to providing a peptide consisting of at most 20 amino acids comprising one or more of the amino acid sequences set forth in SEQ ID NOS: 46-107, 115-185 and 195-587.

In yet still another embodiment, the invention relates to providing a peptide
35 consisting of at most 24 amino acids comprising one or more of the amino acid

sequences set forth in SEQ ID NOS: 46-89, 117-124, 139-157, 163-175 and 195-587.

5 In yet another embodiment, the invention relates to providing a peptide consisting of at most 28 amino acids comprising one or more of the amino acid sequences set forth in SEQ ID NOS: 46-52, 61-66, 73-89, 117-124, 165-175 and 195-587.

10 In still another embodiment, the invention relates to providing a peptide consisting of at most 32 amino acids comprising one or more of the amino acid sequences set forth in SEQ ID NOS: 46-52, 61-66, 73-89, 117-124, 165-175 and 195-587.

15 In still further another embodiment, the invention relates to providing a peptide consisting of at most 36 amino acids comprising one or more of the amino acid sequences set forth in SEQ ID NO: 46-52, 61-66, 73-89, 117- 124, 165-175 and 195-587.

20 In yet another embodiment, the invention relates to providing a peptide consisting of at most 40 amino acids comprising one or more of the amino acid sequences set forth in SEQ ID NO: 46-52, 61-66, 73-89, 117- 124, 165-175 and 195-587.

25 In yet still another embodiment, the invention relates to providing a peptide consisting of at most 44 amino acids comprising one or more of the amino acid sequences set forth in SEQ ID NO: 46-52, 61-66, 73-89, 117- 124, 165-175 and 195-587.

Furthermore, in yet another embodiment, the invention relates to providing a peptide consisting of at least 48 amino acids and at most 224 amino acids comprising one or more of the amino acid sequences set forth in SEQ ID NOS: 2-587.

30 According to amino acid sequences of the above peptides may be derived from the amino acid sequence of polypeptides selected from the group comprising hHBP (SEQ ID NO: 1), pHBP (SEQ ID NO: 588), or human neutrophil elastase (SEQ ID NO: 589).

In one embodiment the peptide comprises at least two of the sequences set forth above. In such embodiment it is preferred that the two or more sequences constitute a continuous sequence derived from another sequence, such as a continuous sequence derived from hHBP, or pHBP, or human neutrophil elastase.

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In another embodiment the peptide comprises at least two of the sequences set forth above. In such embodiment it is preferred that the two or more sequences are randomly selected to constitute a continuous sequence derived from another sequence, such as a random sequence derived from hHBP, or pHBP, or human neutrophil elastase.

10

In the present context by the term "derived from" is meant that one amino acid sequence, such as for example a peptide amino acid sequence, is representing a fragment, or is comprising a fragment of another amino acid sequence, such as for example the amino acid sequence of a larger polypeptide: thus, the peptide amino acid sequence is derived from (originates from) the amino acid sequence of the larger polypeptide.

15

In an additional embodiment the present invention relates to providing a peptide consisting of at least 24 amino acids and at most 224 amino acids comprising one or more of the amino acid sequences set forth in SEQ ID NOS: 233-253.

20

In another additional embodiment the present invention relates to providing a peptide consisting of at least 24 amino acids and at most 224 amino acids comprising one or more of the amino acid sequences set forth in SEQ ID NOS: 286-346.

25

In a preferred embodiment the present invention relates to providing a peptide having the sequence KQGRPFCAGALVHPRFVLTAASCFR set forth in SEQ ID NO: 593, or fragments of said sequence, or variants of said sequence, or fragments of said variants.

30

In another preferred embodiment the present invention relates to providing a peptide having the sequence NQGRHFCCGALIHARFVMTAASCFQ set forth in SEQ ID NO:

594, or fragments of said sequence, or variants of said sequence, or fragments of said variants.

5 By the term of "fragment" in the present context is meant that a peptide of the invention is represented by a shorter amino acid sequence which is identical to any of the amino acid sequences which the peptide comprises.

10 By the term "variant" in the present context is meant that a peptide of the invention is represented by an amino acid sequence which has at least 40% identity with the amino acid sequence of the peptide, more preferably at least 50%, even more preferably at least 60%, even more preferably at least 70%, even more preferably at least 80%, even more preferably at least 90%, even more preferably at least 95%, and most preferably at least 97%.

15 The amino acid sequence of a variant of a peptide may differ from the amino acid sequence of the peptide by an insertion or deletion of one or more amino acid residues and/or the substitution of one or more amino acid residues by different amino acid residues. Preferably, amino acid changes are of a minor nature, that is, conservative amino acid substitutions; small deletions, typically of one to about 10 amino acids; small amino- or carboxyl-terminal extensions; small linker sequences of about 3-15 residues; or a small extension that may facilitates purification by changing net charge or another function, such as a polyhistidine tract, an antigenic epitope or a binding domain.

25 Examples of conservative substitutions are within the group of basic amino acids (such as arginine, lysine and histidine), acidic amino acids (such as glutamic acid and aspartic acid), polar amino acids (such as glutamine and asparagine), hydrophobic amino acids (such as leucine, isoleucine and valine), aromatic amino acids (such as phenylalanine, tryptophan and tyrosine) and small amino acids (such as glycine, alanine, serine, threonine and methionine). Amino acid substitutions, which
30 do not generally alter the specific activity, are known in the art and are described, e.g., by H. Neurath and R.L. Hill, 1979, in, The Proteins, Academic Press, New York. The most commonly occurring exchanges are: Ala/Ser, Val/Ile, Asp/Glu, Thr/Ser, Ala/Gly, Ala/Thr, Ser/Asn, Ala/Val, Ser/Gly, Tyr/Phe, Ala/Pro, Lys/Arg, Asp/Asn, Leu/Ile, Leu/Val, Ala/Glu, Asp/Gly as well as these in reverse.
35

It is an additional aspect of the present invention to provide functional fragments or variants of the peptides.

5 By the term "functional" in relation to a peptide fragment or peptide variant in the present context is meant that the peptide fragment or peptide variant is capable to demonstrate one or more of the biological activities described below.

10 In a preferred embodiment the invention relates to providing functional fragments, variants or fragments of said variants of a peptide having the sequence KQGRPFCAGALVHPRFVLTAASCFR (SEQ ID NO: 593).

15 In another preferred embodiment the invention relates to providing functional fragments, variants or fragments of said variants of a peptide having the sequence NQGRHFCCGALIHARFVMTAASCFQ (SEQ ID NO: 594).

20 It is an object of the invention to provide a peptide, wherein said peptide comprises one or more amino acid sequences set forth in SEQ ID NOS: 233-253 having the motif cys- X_{15} -cys, wherein X_{15} represents an amino acid sequence of 15 amino acids.

25 In a further embodiment said peptide comprises one or more amino acid sequences set forth in SEQ ID NOS: 233-253 and the amino acid sequence set forth in SEQ ID NO: 34.

In yet a further embodiment the present peptide comprises one or more amino acid sequences set forth in SEQ ID NOS: 233-253 and the amino acid sequence set forth in SEQ ID NO: 21.

30 In another aspect the peptide comprises one or more amino acid sequences set forth in SEQ ID NOS: 233-253 and the amino acid sequence set forth in SEQ ID NO: 34 and the amino acid sequence set forth in SEQ ID NO: 21.

Furthermore, it is within the scope of the invention to provide a peptide, which

- i) comprises a sequence derived from any of the amino acid sequences set forth in SEQ ID NO: 1, SEQ ID NO: 588, or SEQ ID NO: 589, and
- ii) is capable of bactericidal activity, and/or
- iii) is an attractant for monocytes.

5

In one embodiment said peptide is consisting of at most 8 amino acids, whereof at least 5 and at most 6 amino acids are basic amino acids selected from the group comprising lysine, arginine and histidine.

10

In another embodiment the peptide is consisting of at most 12 amino acids, whereof at least 6 and at most 9 amino acids are basic amino acids selected from the group comprising lysine, arginine and histidine.

15

In still another embodiment the peptide is consisting of most 16 amino acids, whereof at least 8 and most 12 amino acids are basic amino acids selected from the group comprising lysine, arginine and histidine.

20

In still further another embodiment the peptide is consisting of at the most 20 amino acids, whereof at least 10 and at most 15 amino acids are basic amino acids selected from the group comprising lysine, arginine and histidine.

25

In still yet another embodiment the peptide is consisting of at most 24 amino acids, whereof at least 12 and at most 18 amino acids are basic amino acids selected from the group comprising lysine, arginine and histidine.

30

In yet another embodiment the peptide is consisting of at most 28 amino acids, whereof at least 14 and at most 21 amino acids are basic amino acids selected from the group comprising lysine, arginine and histidine.

In yet further another embodiment the peptide is consisting of at most 32 amino acids, whereof at least 16 and at most 24 amino acids are basic amino acids selected from the group comprising lysine, arginine and histidine.

In yet still further another embodiment the peptide is consisting of at most 36 amino acids, whereof at least 18 and at most 27 amino acids are basic amino acids selected from the group comprising lysine, arginine and histidine.

- 5 In a further another embodiment the peptide is consisting of at most 40 amino acids, whereof at least 20 and at most 30 amino acids are basic amino acids selected from the group comprising lysine, arginine and histidine.

Moreover, the invention also provides a peptide, which

- 10 i) comprises a sequence derived from any of the amino acid sequences set forth in SEQ ID NO: 1, SEQ ID NO: 588, or SEQ ID NO: 589, and
ii) is capable of preventing cell apoptosis.

- 15 In one embodiment said peptide is consisting of at most 8 amino acids, whereof at least 4 and at most 6 amino acids are acidic amino acids selected from the group comprising aspartic acid and glutamic acid.

- 20 In another embodiment the peptide is consisting of at most 12 amino acids, whereof at least 6 and at most 10 amino acids are acidic amino acids selected from the group comprising aspartic acid and glutamic acid.

- 25 In still another embodiment the peptide is consisting of at most 16 amino acids, whereof at least 8 and at most 12 amino acids are acidic amino acids selected from the group comprising aspartic acid and glutamic acid.

- 30 In yet another embodiment the peptide is consisting of at most 20 amino acids, whereof at least 10 and at most 12 amino acids are acidic amino acids selected from the group comprising aspartic acid and glutamic acid.

- In still yet another embodiment the peptide is consisting of at most 24 amino acids, whereof at least 12 and at most 18 amino acids are acidic amino acids selected from the group comprising aspartic acid and glutamic acid.

In yet further another embodiment the peptide is consisting of at most 28 amino acids, whereof at least 14 and at most 21 amino acids are acidic amino acids selected from the group comprising aspartic acid and glutamic acid.

5 In yet still further another embodiment of at most 32 amino acids, whereof at least 16 and at most 24 amino acids are acidic amino acids selected from the group comprising aspartic acid and glutamic acid.

10 Furthermore, in yet still further another embodiment the peptide is consisting of at most 36 amino acids, whereof at least 18 and at most 27 amino acids are acidic amino acids selected from the group comprising aspartic acid and glutamic acid.

15 In a further another embodiment the peptide is consisting of at most 40 amino acids, whereof at least 20 and at most 30 amino acids are acidic amino acids selected from the group comprising aspartic acid and glutamic acid.

Screening assays

20 According to the invention recombinant or synthetically produced peptides are further screened for their biological activity.

25 In the present content by "biological activity of a peptide" is meant that a peptide is able to demonstrate at least one of the following biological activities: (1) heparin binding, (2) lipopolysaccharide (LPS) binding; (3) activating of protein kinase C; (4) stimulating thrombospondin secretion from monocytes; (5) stimulating/inhibiting the production of IL-1, IL-6, IL-8, GCSF, GM-CSF, M-CSF, TNF- α , MCP-1, group Tissue factor, IL-2R- α ; (6) bactericidal; (7) chemotactic for monocytes; (8) anti-apoptotic, (9) stimulating/inhibiting the vascular permeability; (10) stimulating/inhibiting the expression of adhesion molecules PECAM or ICAM1 by endothelial cells, (11) stimulating/inhibiting the production of bradykinin, (12) increase the phagocytic potential, (13) up-regulate class-II MHC.

30

35 In a preferred embodiment the peptide is able to demonstrate at least two of the above activities, more preferably at least three of the above activities, even more preferably at least four of the above activities (1-11), yet even more preferably at

least five of the above activities, even more preferably at least six of the above activities, even more preferably at least seven of the above activities, even more preferably at least eight of the above activities, even more preferably at least nine of the above activities, even more preferably at least ten of the above activities and most preferably the peptide is able to demonstrate at least all of the above activities.

Methods for evaluating of the above listed biological activities of peptides according to the invention are well known in art.

According to the invention there are a number of available assays for evaluating the biological activity of the present peptide.

One of such assays for the evaluation of chemotactic activity of the peptides may for example be the method of Cates et al. (in Leukocyte chemotaxis, p 67. Gallin and Quie eds, Raven Press, NY, 1978), or of Keire et al. (J. Biol. Chem. 2001, 276: 48847-53).

In another embodiment the lipopolysaccharide-binding activity of the peptides may be examined by a method described by Linde et al (Biotechniques 2000, 28:218-20).

To evaluate the bactericidal activity of the present peptides, the assay described by Shafer et al. (Infect. Immun. 1986, 53:651-55) may be used.

In one aspect measuring cell apoptosis in the presence of the present peptides may be done according to Linde et al. (Anal. Biochem. 2000, 280:186-8).

It is possible to perform an evaluation of the heparin binding capacity of the peptides by conventional chromatography on a commercially available heparin-affinity column.

The protein kinase C activation by the peptides may be done according to Pereira et al., 1996 (J. Leukoc. Biol. 60:415-22).

The changes in expression of different polypeptides, such as for example IL-1, IL-6, IL-8, TNF- α , thrombospondin, PECAM or ICAM in the presence of the peptides according to the invention may, for example, be evaluated either by reverse phase

transcriptase, immunoassay, immunoblotting, or immunostaining of the treated cells grown in culture.

5 The vascular permeability may be determined by using the assay as described by Gautam et al. in 1998 (Br J Pharmacol 1998 Nov;125(5):1109-14)

Medicament

10 It is an important objective of the present invention to use the peptides, functionally active fragments or variants of said peptides for the manufacture of a medicament for prevention and/or treatment of Gram positive and/or Gram negative infections, sepsis, severe sepsis, septic shock and/or disseminated intravascular coagulation, and/or for modulation of inflammatory response, and/or prevention of cell apoptosis.

15 In one embodiment the invention relates to the manufacture of a medicament which is capable of being used for prevention and/or treatment of Gram positive bacterial infection caused by Bacillaceae, Micrococcaceae, Mycobacteriaceae, Peptococcaceae and/or a Gram negative bacterial infection caused by Acetobacteriaceae, Alcaligenaceae, Bacteroidaceae, Chromatiaceae, Entero-
20 bacteriaceae, Legionellaceae, Neisseriaceae, Nitrobacteriaceae, Pseudomonadaceae, Rhizobiaceae, Rickettsiaceae, Spirochaetaceae, Vibrionaceae, Brucella, Chromobacterium.

25 In a preferred embodiment for prevention and/or treatment the infection by *Neisserie meningitidis* (meningococcus) and/or *Pneumococcus pneumoniae* (pneumococcus).

In another embodiment the invention relates to the manufacture of a medicament which is capable of being used for prevention and/or treatment of sepsis, severe sepsis, septic shock and disseminated intravascular coagulation.

30 It is an important objective of the invention to use the peptides for the manufacture of a medicament for stimulation of an inflammatory response, in a preferred embodiment, the inflammatory response to bacterial infection.

Another important objective of the invention is to use the peptides for the manufacture of a medicament for inhibition of an inflammatory response. Examples of inflammatory responses, which may be harmful for an individual and therefore are advantageously being suppressed include but are not limited by conditions associated with extensive trauma, or chronic inflammation, such as for example type IV delayed hypersensitivity, associated for example with infection by *Tubercle bacilli*, or systematic inflammatory response syndrome, or multiple organ failure, or rheumatoid arthritis.

In an additional embodiment of the invention to use the peptides capable of anti-apoptotic activity are used for the manufacture of a medicament for the treatment of a disease, pathological conditions whereof are associated with massive cell loss due to apoptosis. Examples of such a disease include but not limited by degenerative diseases the central and peripheral nervous system, such as postoperative nerve damage, traumatic nerve damage, e.g. resulting from spinal cord injury, impaired myelination of nerve fibers, postischaemic damage, e.g. resulting from a stroke, multiinfarct dementia, multiple sclerosis, nerve degeneration associated with diabetes mellitus, neuro-muscular degeneration, schizophrenia, Alzheimer's disease, Parkinson's disease, or Huntington's disease, degenerative conditions of the gonads, of the pancreas, such as diabetes mellitus type I and II, of the kidney, such as nephrosis, or cancer.

By the term "apoptosis" in the present content is meant a programmed cell death due to activation an internal death program.

In the pharmaceutical composition of a medicament of the invention, the peptides and antibodies may be formulated by any of the established methods of formulating pharmaceutical compositions, e.g. as described in Remington's Pharmaceutical Sciences, 1985. The composition may typically be in a form suited for local or systemic injection or infusion and may, as such, be formulated with sterile water or an isotonic saline or glucose solution. The compositions may be sterilised by conventional sterilisation techniques, which are well known in the art. The resulting aqueous solutions may be packaged for use or filtered under aseptic conditions and lyophilised, the lyophilised preparation being combined with the sterile aqueous solution prior to administration. The composition may contain pharmaceutically acceptable auxiliary

substances as required to approximate physiological conditions, such as buffering agents, tonicity adjusting agents and the like, for instance sodium acetate, sodium lactate, sodium chloride, potassium chloride, calcium chloride, etc. The concentration of peptides may vary widely, i.e. from less than about 0.5%, such as from 1%, to
5 as much as 15-20% by weight. A unit dosage of the composition may typically contain from about 10 mg to about 1 g of a peptide.

The peptides and antibodies may be administered topically or by injection. Dosages will be prescribed by the physician according to the particular condition and the particular individual to be treated. Dosages and frequency is carefully adapted and adjusted according to parameters determined by the physician in charge. A preferred
10 administration route may be e.g. subcutaneous injections. Subcutaneous, intravenous, intramuscular, intratracheal, intravesical, intratechal or intraperitoneal injections of HBP peptides and anti-HBP antibodies may be given per 24 hours in the
15 range of from 0.1-100 mg, especially 0.1-20 mg, in particular 0.1-10 mg per kg body weight. The dose may be given 1-4 times per 24 hours or administered continuously through a catheter.

Compositions of a medicament used in the present invention comprising bioactive peptides of HBP, HBP homologous peptides or anti-HBP antibodies described below may additionally be supplemented by antibiotics, wherein said antibiotics are routinely prescribed antibiotics by the physician according to the particular condition and the particular individual to be treated. In a preferred embodiment the supplemented antibiotics are selected from but not limited by the group of beta-lactam antibiotics, comprising penicillins and cephalosporins. A medicament comprising a
20 peptide of HBP or a fragment of a HBP homologous peptide or an anti-HBP antibody may still additionally be supplemented by a pro-inflammatory drug, or an anti-inflammatory drug, wherein said drugs are prescribed by the physician according to the particular condition and the particular individual to be treated. The supplementary pro-inflammatory drugs may for example be selected from the group comprising
25 CSF (colony stimulating factor) drugs. The supplementary anti-inflammatory drugs may for example be selected from the group comprising antibiotics, steroids, cytostatics, or antiviral drugs.

35 HBP receptors and binding sites

According to the invention information concerning potential HBP receptors and binding sites is aiding the selection of the present peptides. There has been no identification of a HBP receptor, but receptor-like structures or binding sites of HBP have been identified. HBP is a dipole separated by a hydrophobic cleft and it is therefore capable to interact with both positively and negatively charge surfaces and molecules and with hydrophobic molecules and epitomes. The charged surface areas (the epitomes) of HBP are important for several of its functions. Without being bound by theory some of such functions are described below:

It has been demonstrated that HBP's positively charged epitomes bind to negatively charged macromolecules such as the heparan sulphate and chondroitin sulphate side chains of the proteoglycans (Olofsson, AM. et al. 1999), which are present at the surface of nearly every adherent mammalian cells. Proteoglycans are proteins with long carbohydrate chains of the glucosaminoglycans (GAG) type attached. They have recently been recognized as an important part of the signaling mechanism between cells. The proteoglycans are today recognized as co-receptors that can influence how e.g. the growth factor interacts with its receptor. Co-receptors affect which signal molecules bind to the receptor, how strong the interaction is or how far the signal spreads. Co-receptors regulate such decisions as when the cell divides, what type of proteins it manufactures and even if it should die. HBP has been shown to bind to the carbohydrate part (e.g. heparan sulphate) of the syndecan family of proteoglycans, which play an important role in internalization of proteins. The binding of HBP to such proteoglycans lead to uptake of HBP into endothelial cells (Olofsson, AM et al.,1999) and probably other cell types as well. Heparan sulphate and similar highly charged negative molecules of the glucosaminoglycan type may therefore serve as binding sites for HBP, mediating many of its diverse regulatory functions. In this context it is should be noted that heparan sulphate and similar glucosaminoglycans are not just simple negatively charged molecules mediating a non-specific ionic interaction. In contrast e.g. the heparan sulphate are synthesized such that very diverse and subtle variations in the structure are achieved. Accordingly, the synthesized heparan sulphate molecules may fit only very specific positively charged epitopes, such as the ones found on the surface of HBP. The heparan sulphates and similar proteoglycans with GAG side chains may therefore be seen as a proper receptor or co-receptor for HBP.

HBP may also exploit its dipolar nature by activating the contact phase system. The contact phase system consists of HMWK and three other proteins which are closely bound together on the cell surface. HMWK is a large protein consisting of 6 domains, of which one (domain 4) contains the Bradykinin sequence. An electrostatic binding from a positively charged histidin-rich area in domain 5 of HMWK to negatively charged heparan sulphate (Renne, T. et al., 2000) and chondroitin sulphate (Renne, T. et al., 2001) proteoglycans contribute significantly to the binding of HMWK to cell surfaces. The activation of the contact phase system requires that the individual components (HMWK, fXII and pre-kallikrein) are brought in close contact to each other and probably also that certain conformational changes are induced. Heparin-binding protein (HBP) has been shown to play a pivotal role in activating the contact phase system (Gautam, N. 2001), and to be capable of highly effectively displacing HMWK from GAG in an in vitro model (Renne, T. 1999). This occurs most likely by formation of two electrostatic bindings, one between the negatively charged GAG on the cell surface and HBP's strongly positively charged surface area, and another between the positively charged domain 5 of HMWK and HBP's negatively charged surface area.

Further, in addition to the above-mentioned highly charged binding sites HBP also carries other putative binding sites, such as binding sites for the Lipid A part in LPS and for interaction with and activation of Protein Kinase C (PKC), see Iversen 1997 for a review.

Monofunctional HBP peptides

The peptides according to the invention having agonistic or antagonistic properties to the putative binding sites for HBP are of considerable pharmaceutical interest as drug candidates for the prevention and/or the treatment of infections, local and systemic inflammatory disorders, asthma, systemic inflammatory response syndrome (SIRS), degenerative diseases (Alzheimer's disease), pain and other serious diseases and disorders (see table 1 in the Experimental section).

As outlined above HBP is by nature designed for initiation and regulation of local inflammatory defense to invading bacteria. In the situation of a local infection intact HBP is an ideal molecule for initiating, coordinating and regulating all the many dif-

ferent protecting mechanisms against the invading bacteria. In such situation a virulent inflammatory defense as initiated by HBP is fully appropriate and is probably needed to ensure survival of the individual. In agreement with this presumed beneficial effect of HBP, intact HBP has in animal studies been shown to be useful in prevention and treatment of severe life threatening infections and sepsis. However, in a therapeutic situation (by therapeutic is here to be understood both preventive and proper therapeutic interventions) HBP is administered differently from the natural way and therefore not all of its multiple effects may be needed or desirable.

Peptides with only one or some of the intact HBP molecule functions may therefore have significant advantages compared to the intact HBP for the treatment of specific conditions because they may be more specific, have different threshold for activation by a given process or be more powerful (displaying higher maximal efficacy).

Further, it is within the scope of the invention to provide peptides having a single function, i.e. mono-functional peptides, inhibiting specific HBP mediated processes. Below is a description of therapeutic applications, wherein the present peptides may be employed.

In the treatment of severe life threatening infections with HBP the monocyte activating and stimulating function may be the most important. To treat a lung infection for instance, HBP will most likely have to be administered systemically (e.g. as a subcutaneous injection or infusion). When administered at a site distant from the infection the ability of intact HBP to induce capillary leakage may not be advantageous, since this could lead to accumulation of neutrophils and edema formation at the administration site. While such potential side effect may be fully acceptable considering the ability of HBP to prevent or treat life-threatening infections, the use of a mono-functional HBP peptide according to the invention is to be preferred. The mono-functional peptide may have an increased ability to activate monocytes and a decreased ability to induce capillary leakage.

Monocytes play a significant role not only in eliminating bacteria but also in eliminating certain cancer cells. A mono-functional peptide with increased efficacy for stimulating the cytotoxic ability of the monocytes and macrophages would be highly desirable.

Many degenerative diseases (e.g. Alzheimer's disease) are characterized by an increased program cell death – i.e. and increased apoptosis. This means, that the cells die faster. Agents preventing or delaying apoptosis could conceivably be of use for slowing down the development of such degenerative diseases. A mono-

5 functional peptide of the invention having a high anti-apoptosis efficacy, but no inflammatory potential may be a potential candidate for intervention in degenerative diseases.

Further, while the inflammatory defense initiated and regulated by intact HBP is needed to insure elimination of local bacterial infections it is not ideally designed to combat systemic infections, which spread to the whole body. In such circumstances, the inflammatory response may lead to damages to the organs and even to death of the organism if not controlled or stopped in time. Furthermore, the organism may react with an inflammatory response in situations where there is no infection. In such

10 situations the inflammatory response is not only needless it is also highly damaging to the body. As an example, patients exposed to a trauma e.g. a car accident may develop a systemic inflammatory response caused by the extensive tissue damage. This may lead to hypotension, activation of the coagulation system, formation of clots and subsequent bleeding due to increased fibrinolysis, respiratory distress and failure of vital organs, such as the liver, kidney and the heart. The mechanisms leading to such Systemic Inflammatory Response Syndrome (SIRS) and Multiple Organ Failure (MOF) have not been fully elucidated. Without being bound by theory the interaction and contribution of HBP to the activation of the contact phase system probably plays a significant role.

15 20 25

According to the invention it is of significant interest to provide antagonist to HBP to use in the prevention and/or the treatment of such serious disorders. While antibodies to HBP may be highly useful in several clinical situations characterized by increased activation of the contact phase system and increased Bradykinin release,

30 small peptide HBP antagonists may have several advantages. They may be used in a wider range of diseases and disorders due to their smaller size and presumed better tissue penetration.

In another aspect of the present invention a more effective means of preventing bradykinin mediated disease processes is provided. As mentioned above anti-HBP

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antibodies are obvious candidates, but small peptide HBP antagonists of the invention may have significant advantages. Bradykinin plays a role in the development of SIRS amongst other diseases. Bradykinin exerts its effect by interaction with specific receptors. Numerous bradykinin antagonists have been synthesized in the search for new drugs, which can prevent the action of bradykinin in conditions, such as circulatory and endotoxic shock, rhinitis and other allergic conditions, chronic inflammatory diseases such as rheumatoid arthritis, and colitis ulcerosa and brain edema. Although some of them have shown to be of some clinical use the effect has in general been less than expected considering the central mediator role of bradykinin. Without being bound by theory one reason might be that an antagonist only partly blocks the effect of bradykinin, but probably more likely that the antagonist in a therapeutic situation is often given after a significant amount of bradykinin has been released and has exerted its effects on the receptors.

In a further aspects of the present invention mono-functional, non-toxic agonists which bind LPS or other endotoxins, such as PGN, LTA or other cell wall components from bacteria with the same or higher affinity as Polymyxin B would have significant therapeutic potential for the treatment of sepsis. Endotoxins from both Gram negative (LPS) and Gram positive (PGN, LTA) bacteria play a significant role in the development of septic shock. It has recently been shown that removal of endotoxin (LPS) from the blood of septic patient by passage of the patient's blood through a Polymyxin B – column significantly reduces mortality. Polymyxin B binds LPS. Polymyxin B has certain structural similarities with HBP, which also binds LPS.

Production

The peptides of the present invention may be prepared by conventional synthetic methods, recombinant DNA technologies, enzymatic cleavage of full-length proteins which the peptide sequences are derived from, or a combination of said methods.

Synthetic preparation

The methods for synthetic production of peptides are well known in art. Detailed descriptions as well as practical advice for producing synthetic peptides may be found in Synthetic Peptides: A User's Guide (Advances in Molecular Biology), Grant G. A. ed., Oxford University Press, 2002, or in: Pharmaceutical Formulation: Devel-

opment of Peptides and Proteins, Frokjaer and Hovgaard eds., Taylor and Francis, 1999.

Peptides may for example be synthesised by using Fmoc chemistry and with Ac-protected cysteins. After purification by reversed phase HPLC, peptides may be further processed to obtain for example cyclic or C- or N-terminal modified isoforms. The methods for cyclization and terminal modification are well-known in the art and described in detail in the above cited manuals.

The DNA sequence encoding a peptide or full-length protein of the invention may be prepared synthetically by established standard methods, e.g. the phosphoramidite method described by Beaucage and Caruthers, 1981, Tetrahedron Lett. 22:1859-1869, or the method described by Matthes et al., 1984, EMBO J. 3:801-805. According to the phosphoramidite method, oligonucleotides are synthesized, e.g. in an automatic DNA synthesizer, purified, annealed, ligated and cloned in suitable vectors.

Recombinant preparation

The peptides of the invention may also be produced by use of recombinant DNA technologies. The DNA sequence encoding a peptide may be prepared by fragmentation of the DNA sequences encoding a full-length protein, which the peptide is derived from, using DNAase I according to a standard protocol (Sambrook et al., Molecular cloning: A Laboratory manual. 2rd ed., CSHL Press, Cold Spring Harbor, NY, 1989). The present invention relates to the full-length protein being selected from the group of proteins comprising human HBP (SEQ ID NO:1), porcine HBP (SEQ ID NO: 588) and human neutrophil elastase (SEQ ID NO: 589), said proteins being encoded by the DNA sequences set forth in SEQ ID NO: 590, SEQ ID NO: 591 and SEQ ID NO: 592, correspondingly. The DNA encoding the full-length proteins may alternatively be fragmented using specific restriction endonucleases. The fragments of DNA are further purified using standard procedures described in Sambrook et al., Molecular cloning: A Laboratory manual. 2rd ed., CSHL Press, Cold Spring Harbor, NY, 1989.

The DNA sequence encoding a full-length protein may also be of genomic or cDNA origin, for instance obtained by preparing a genomic or cDNA library and screening

for DNA sequences coding for all or part of the full-length protein by hybridization using synthetic oligonucleotide probes in accordance with standard techniques (cf. Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Ed., Cold Spring Harbor, 1989). The DNA sequence may also be prepared by polymerase chain re-
5 action using specific primers, for instance as described in US 4,683,202 or Saiki et al., 1988, *Science* 239:487-491.

The DNA sequence is then inserted into a recombinant expression vector, which may be any vector, which may conveniently be subjected to recombinant DNA pro-
10 cedures. The choice of vector will often depend on the host cell into which it is to be introduced. Thus, the vector may be an autonomously replicating vector, i.e. a vector that exists as an extrachromosomal entity, the replication of which is independent of chromosomal replication, e.g. a plasmid. Alternatively, the vector may be one which, when introduced into a host cell, is integrated into the host cell genome and
15 replicated together with the chromosome(s) into which it has been integrated.

In the vector, the DNA sequence encoding a peptide or a full-length protein should be operably connected to a suitable promoter sequence. The promoter may be any DNA sequence, which shows transcriptional activity in the host cell of choice and
20 may be derived from genes encoding proteins either homologous or heterologous to the host cell. Examples of suitable promoters for directing the transcription of the coding DNA sequence in mammalian cells are the SV 40 promoter (Subramani et al., 1981, *Mol. Cell Biol.* 1:854-864), the MT-1 (metallothionein gene) promoter (Palmiter et al., 1983, *Science* 222: 809-814) or the adenovirus 2 major late pro-
25 moter. A suitable promoter for use in insect cells is the polyhedrin promoter (Vasuvedan et al., 1992, *FEBS Lett.* 311:7-11). Suitable promoters for use in yeast host cells include promoters from yeast glycolytic genes (Hitzeman et al., 1980, *J. Biol. Chem.* 255:12073-12080; Alber and Kawasaki, 1982, *J. Mol. Appl. Gen.* 1: 419-434) or alcohol dehydrogenase genes (Young et al., 1982, in *Genetic Engineering of Mi-
30 croorganisms for Chemicals*, Hollaender et al., eds., Plenum Press, New York), or the TPI1 (US 4,599,311) or ADH2-4c (Russell et al., 1983, *Nature* 304:652-654) promoters. Suitable promoters for use in filamentous fungus host cells are, for in-
stance, the ADH3 promoter (McKnight et al., 1985, *EMBO J.* 4:2093-2099) or the tpiA promoter.

The coding DNA sequence may also be operably connected to a suitable terminator, such as the human growth hormone terminator (Palmiter et al., op. cit.) or (for fungal hosts) the TPI1 (Alber and Kawasaki, op. cit.) or ADH3 (McKnight et al., op. cit.) promoters. The vector may further comprise elements such as polyadenylation signals (e.g. from SV 40 or the adenovirus 5' Elb region), transcriptional enhancer sequences (e.g. the SV 40 enhancer) and translational enhancer sequences (e.g. the ones encoding adenovirus VA RNAs).

The recombinant expression vector may further comprise a DNA sequence enabling the vector to replicate in the host cell in question. An example of such a sequence (when the host cell is a mammalian cell) is the SV 40 origin of replication. The vector may also comprise a selectable marker, e.g. a gene the product of which complements a defect in the host cell, such as the gene coding for dihydrofolate reductase (DHFR) or one which confers resistance to a drug, e.g. neomycin, hydromycin or methotrexate.

The procedures used to ligate the DNA sequences coding the peptides or full-length proteins, the promoter and the terminator, respectively, and to insert them into suitable vectors containing the information necessary for replication, are well known to persons skilled in the art (cf., for instance, Sambrook et al., op.cit.).

To obtain recombinant peptides of the invention the coding DNA sequences may be usefully fused with a second peptide coding sequence and a protease cleavage site coding sequence, giving a DNA construct encoding the fusion protein, wherein the protease cleavage site coding sequence positioned between the HBP fragment and second peptide coding DNA, inserted into a recombinant expression vector, and expressed in recombinant host cells. In one embodiment, said second peptide selected from, but not limited by the group comprising glutathion-S-reductase, calf thymosin, bacterial thioredoxin or human ubiquitin natural or synthetic variants, or peptides thereof. In another embodiment, a peptide sequence comprising a protease cleavage site may be the Factor Xa, with the amino acid sequence *IEGR*, enterokinase, with the amino acid sequence *DDDDK*, thrombin, with the amino acid sequence *LVPR/GS*, or *Acharombacter lyticus*, with the amino acid sequence *XXK*, cleavage site.

Host cell

The host cell into which the expression vector is introduced may be any cell which is capable of expression of the peptides or full-length proteins, and is preferably a eukaryotic cell, such as invertebrate (insect) cells or vertebrate cells, e.g. *Xenopus laevis* oocytes or mammalian cells, in particular insect and mammalian cells. Examples of suitable mammalian cell lines are the HEK293 (ATCC CRL-1573), COS (ATCC CRL-1650), BHK (ATCC CRL-1632, ATCC CCL-10) or CHO (ATCC CCL-61) cell lines. Methods of transfecting mammalian cells and expressing DNA sequences introduced in the cells are described in e.g. Kaufman and Sharp, J. Mol. Biol. 159, 1982, pp. 601-621; Southern and Berg, 1982, J. Mol. Appl. Genet. 1:327-341; Loyter et al., 1982, Proc. Natl. Acad. Sci. USA 79: 422-426; Wigler et al., 1978, Cell 14:725; Corsaro and Pearson, 1981, in Somatic Cell Genetics 7, p. 603; Graham and van der Eb, 1973, Virol. 52:456; and Neumann et al., 1982, EMBO J. 1:841-845.

Alternatively, fungal cells (including yeast cells) may be used as host cells. Examples of suitable yeast cells include cells of *Saccharomyces spp.* or *Schizosaccharomyces spp.*, in particular strains of *Saccharomyces cerevisiae*. Examples of other fungal cells are cells of filamentous fungi, e.g. *Aspergillus spp.* or *Neurospora spp.*, in particular strains of *Aspergillus oryzae* or *Aspergillus niger*. The use of *Aspergillus spp.* for the expression of proteins is described in, e.g., EP 238 023.

Culture medium

The medium used to culture the cells may be any conventional medium suitable for growing mammalian cells, such as a serum-containing or serum-free medium containing appropriate supplements, or a suitable medium for growing insect, yeast or fungal cells. Suitable media are available from commercial suppliers or may be prepared according to published recipes (e.g. in catalogues of the American Type Culture Collection).

The peptides or full-length proteins recombinantly produced by the cells may then be recovered from the culture medium by conventional procedures including separating the host cells from the medium by centrifugation or filtration, precipitating the proteinaceous components of the supernatant or filtrate by means of a salt, e.g. ammonium sulphate, purification by a variety of chromatographic procedures, e.g. HPLC, ion exchange chromatography, affinity chromatography, or the like.

Experimentals

Identification of and screening for active HBP peptide sequences

5 Any HBP peptide sequence with 4 or more amino acid residues may be able to exercise an agonistic or antagonistic function against one or more of HBP putative binding sites or receptors (for simplicity just called HBP receptors below). However, certain sequences and surface areas may be identified as more interesting than others. Several measures to identify potentially interesting sequences with agonistic
10 or antagonistic functions to HBP receptors were taken.

Firstly, the peptide sequence of HBP and proteins closely similar to HBP within the same species i.e. Homo sapiens were investigated. HBP is structurally very similar to human neutrophil elastase (hHNE), and specific HBP functions may be found in
15 the areas of human HBP, which are non identical to the sequences of hHNE, i.e. in the areas of the HBP molecule, which have not been conserved during evolution.

Secondly, it is hypothesized that such peptide sequences in HBP, which are conserved between species might be of particular interest.

20 Thirdly, it is hypothesized that sequences in other species than Homo sapiens e.g. the pig which are closely similar but not identical to the corresponding human sequence might have other abilities than the human sequence, e.g. be antagonistic instead of agonistic.

25 Finally, it is hypothesized that among the sequences identified as outlined above, the more interesting sequences may have to be found on the surface of the molecule. As the two more important known receptor-like surface areas (epitopes) are both highly charged it is hypothesized that sequences with high density of charged
30 amino acids would be of particular interest.

Screening of HBP peptide sequences for biological activity

Among the many sequences identified by the above approach, only some will have desirable biological and pharmaceutical functions. The number of possible combinations (i.e. different amino acid sequences) is astronomical. As an example the theo-
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retical number of different peptides consisting of 25 amino acids is $3.36 * 10^{32}$. Even though some sequences based on the above outlined considerations can be identified as more interesting than others, a high number of different peptides will have to be screened for interesting biological and pharmaceutical properties.

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It is therefore important to have highly reliable high capacity assay systems to identify HBP peptides and analogues hereof with pharmaceutical potential. In this context it should be realized that testing of peptides to be useful for preventive or therapeutic purposes in humans, should be done in a human system. Intact HBP from one species does not necessarily react identical in other species and use of an animal test system e.g. a rat system for screening of the biological functions of an HBP derived peptide to be used in humans could easily be misleading. Below examples on screening assays to be used for identification of peptides with pharmaceutical potential for prevention and treatment of infectious diseases (e.g. pneumonia), severe inflammatory disorders (e.g. SIRS) and degenerative disorders (e.g. Alzheimer's disease) are presented.

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Example 1: Screening for inflammatory and anti-inflammatory potential of HBP derived peptide.

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Human whole blood (WB) contains besides red cells, platelets and plasma the white blood cells including the neutrophils and monocytes. Neutrophils and monocytes have receptors for bacterial products such as LPS, PGN and LTA. The bacterial products react directly or via specific binding proteins to receptors on the monocytes thereby stimulating them to secrete and release inflammatory cytokines comprising, but not limited to IL-1, IL-6, and TNF- α . HBP has in itself no measurable effect on cytokine secretion, but significantly amplifies cytokine synthesis and secretion induced by bacterial products. In the assay type described the amplification of 160 μ mol HBP per ml WB in general leads to at least three-fold amplification of the cytokine secretion.

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In the example to be described LPS from the E. coli is used to stimulate the monocytes in WB (anti-coagulated by use of citrate) and the activity is measured by subsequently quantifying IL-6 in plasma separated from WB. The activity of HBP, HBP derived peptides and analogues hereof are evaluated by their ability to:

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1. increase IL-6 secretion in absence of bacterial products
2. increase IL-6 secretion in presence of bacterial products
3. decrease IL-6 secretion in presence of bacterial products
- 5 4. inhibit amplification of cytokine secretion induced by intact HBP

10 An ideal HBP peptide agonist will display the same ability as intact HBP itself in this system, i.e. it will have no activity itself when added to WB but when added simultaneously with LPS or another bacterial product it should stimulate the IL-6 secretion with a factor of at least 3, preferably 4 or more. If the peptide itself stimulates IL-6 secretion in options or of LPS or other bacterial products, it may lead to a systemic hyper-inflammation in organism which is not desirable.

Reagents and methods

- 15 All operations must be carried out in LAF cabinet by observance of stringent aseptic techniques. All test tubes, pipette tips etc. must be pyrogen-free. Buffers must be prepared by use of sterile, pyrogen water, preferably water for injection. Use 0.1 % pyrogen-free BSA/PBS for all dilutions.
- 20 Add 20 µl of HBP derived peptide (in concentrations from 25 to 2500 µM) to 100 µl freshly drawn (less than 4 hours old) citrate whole blood from a healthy human volunteer. Add 20 µl bacterial component (LPS, LTA or PGN) in concentrations from 5 to 5000 ng/ml, preferably 50 to 500 ng/ml. Mix well and incubate for 16-18 hours in an atmosphere of 5 % carbon dioxide and at least 95 % relative humidity. At the end
- 25 of the incubation add at least 5 volumes (700 µl) 0.1 % BSA/PBS. Mix well. Centrifuge 10 min. at 10.000 g. Aspirate 500 µl supernatant. Determine the level of IL-6 by a specific human immune assay for human IL-6 with sensitivity of at least 3 pg/ml, e.g. Human IL-6 Kit from RnD Systems (cat. no. D 6050).
- 30 Negative controls: 100 µl WB plus 40 µl 0.1 % BSA/PBS. Positive control: 100 µl WB plus 20 µl LPS (same concentration as used for testing the peptide) and 20 µl 0.1 % BSA/PBS.

Example 2: Screening for anti-apoptotic potential of HBP derived peptides and analogues

5 The screening for anti-apoptotic peptides is carried out essentially as described by Shrotri MS. et al., 2000.

Isolation of human neutrophils (PMNs)

10 Peripheral blood from normal volunteers was collected and PMNs were separated by density gradient using Ficoll-Hypaque (Sigma Chemical Co.). PMNs obtained were divided into 1-ml samples with 3.0×10^6 cells/ml and were treated and analyzed as per the protocols described below.

Cell Fixation and Staining Protocol for Analysis of Apoptosis

15 Cell pellets were obtained by centrifugation at 300g and fixed with 1% paraformaldehyde for 15 min at 4°C. Cells were washed twice and permeabilized with 70% ice-cold ethanol and stored at -20°C. Cells samples were washed twice and stained by the terminal dUTP nick-end labeling (TUNEL) assay using the APO-BRDU kit (Phoenix Flow Systems, San Diego, CA), following the manufacturer's instructions.

20 Briefly, in this assay, the enzyme terminal deoxynucleotidyl transferase (TdT) catalyzes the addition of nucleotides to DNA strand breaks in the apoptotic cells, which are subsequently labeled with fluorescein isothiocyanate (FITC)-conjugated antinucleotide antibodies. The fluorescent cells are the apoptotic cells that are then identified or assessed using the flow cytometer (EPICS Elite, Beckman-Coulter, Hialeah,

25 FL). These apoptotic cells were also visually confirmed by confocal microscopy (Meridian Instruments Inc., Okemos, MI).

30 *Time zero group.* Certain samples were fixed immediately after isolation, permeabilized, and stored at -20°C for TUNEL assay, as described earlier. These samples were designated as time zero, in which no culturing was involved.

24-h culture groups. Certain samples were re-suspended after isolation in 10% fetal bovine serum (serum-enriched group) with 25 µg of control protein (BSA) or 25 µg of HBP per ml. sample. Samples were incubated in 0% serum or RPMI (serum-deprived group) with control protein, HBP or HBP derived peptide. After 24 h culture

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in a humidified CO₂ incubator, cells were fixed, permeabilized, and stored at 220°C for later TUNEL assay, as described above.

Identification of anti-apoptotic peptides

5 Addition of 25 µg HBP per ml sample typically decreases apoptosis from about 70 % to 45 %. Peptides decreasing apoptosis to the same or greater extent when used in equimolar amounts should be considered anti-apoptotic.

Example 3: Identification of a highly potent anti-inflammatory HBP peptide

10 As an example on the use of the methods outlined above to predict an HBP peptide sequence it is disclosed how a highly anti-inflammatory novel HBP peptide sequence is identified.

15 The innate immune response is activated by pattern recognition receptors (toll like receptors) on monocytes, neutrophils and other immune cells. HBP increase the sensitivity of these pattern recognition receptors for their response to the specific pattern motifs on the cell wall of both gram negative and gram positive bacteria as well as on fungi and other infective agents. Serine proteases and more important serine proteases with mutations in the catalytic site, but with a highly conserved serine protease fold such as HBP, play a pivotal role in innate immunity. Invertebrates have only innate immune response as the specific immune system was first developed with the evolution of the bonefish. Several serine proteases with mutations in the active site has been studied in a number of invertebrates and the *Trichoplusia ni* larval has an HBP-like serine protease. The hallmark in the mutation in the active site in the HBP from man, pig and *Trichoplusia ni* is an Histidin (H) to Serine (S) mutation, a conserved Aspartic acid (D) whereas the Serine (S) mutation is random. The active site with these mutations is therefore highly likely involved in the mechanism of action of the HBP family.

30 Method

In the present context the term "h20-44" covers the human heparin binding protein sequence of amino acids numbers 20-44. Further, by the term "p20-44" is meant the porcine heparin binding protein sequence of amino acids numbers 20-44.

The human (h20-44) and porcine (p20-44) peptides were synthesized and tested in the screening assay described in Example 1. The following parameters were examined: (a) ability to induce inflammation on their own (i.e. in the absence of any bacterial component), (b) ability to amplify or inhibit inflammation induced by a bacterial component, such as LPS from the Gram negative bacteria *E. coli* and PGN or Purified Cell Wall (PCW) from a Gram positive bacteria. As measure for immune stimulation secretion of the release of IL-6 in citrated whole blood was used. The peptides were tested in the concentrations 0.09, 0.18, 0.36 and 0.71 mg/ml blood. LPS was used at the concentration 100 ng/ml blood and PGN and PCW were used at 50 µg/ml blood.

Results

Human HBP 20-44 peptide induced a significant and dose-dependent increase in IL-6 secretion, whereas porcine HBP 20-44 displayed no significant or dose-dependent effect (see Figure 1).

In blood stimulated with 100 ng/ml LPS, human HBP 20-44 did not significantly increase the IL-6 secretion up to 0.36 mg/ml peptide. At 0.71 mg/ml, human HBP 20-44 increased IL-6 secretion significantly, but the effect of human HBP 20-44 and LPS together was slightly less (12,130 pg/ml) than the sum of the IL-6 secretion induced by LPS and human HBP 20-44 individually (14,178 pg/ml) (see Figure 2). In contrast porcine HBP 20-44 peptide significantly and dose-dependently inhibited the LPS induced IL-6 secretion.

In blood stimulated with PGN (50 µg/ml) from *Staphylococcus aureus* human HBP 20-44 increased IL-6 secretion in dose-dependent way (see Figure 3). In contrast porcine HBP 20-44 peptide significantly and dose-dependently inhibited the PGN induced IL-6 secretion.

In blood stimulated with PCW (50 µg/ml) from *Staphylococcus aureus* human HBP 20-44 increased IL-6 secretion in dose-dependent way (Figure 4). In contrast porcine HBP 20-44 peptide significantly and dose-dependently inhibited the PCW induced IL-6 secretion.

Conclusion

Human HBP 20-44 peptide surprisingly by itself significant stimulate secretion of the pro-inflammatory cytokine IL-6. In the presence of bacterial components human HBP 20-44 to some extent further increases the immune stimulation induced by the bacterial products. Human HBP 20-44 has previously been thought to act via its ability to bind to LPS and was presumed to be an LPS neutralizing agent. An LPS neutralizing agent would inhibit the immune response, but here it is shown that human HBP 20-44 is instead a powerful immune stimulating agent. In contrast the structurally very similar porcine HBP 20-44 peptide, which only deviates from its human counterpart by 7 amino acid substitutions was found to be a highly potent anti-inflammatory agent, which significantly decreases inflammation induced by bacterial components from both Gram negative and Gram positive bacteria. Porcine HBP 20-44 peptide thus holds significant potential for becoming a broadly applicable anti-inflammatory agents with indications ranging form treatment of chronic inflammatory diseases over re-perfusion injuries in myocardial and brain insults to the life-threatening systemic inflammatory response syndrome.

Example 4: Modification of the C-terminal and N-terminal amino acid residues in hHBP and pHBP.

In human blood stimulated with 250 ug/ml PGN from *S. aureus*, hHBP 20-44 acetylated at the N-terminal amino group and amidated at the C-terminal carboxyl group stimulated the IL-6 secretion in a dose dependant way (figure 5). In figure 5 the IL-6 response has been normalized to the effect of PGN alone. Compared to figure 2 it appears that there is a more than ten fold stimulation of the PGN mediated IL-6 production for the N- and C-terminal substituted peptide.

Example 5: Essential amino acid residues in hHBP and pHBP involved in regulation of IL-6 production.

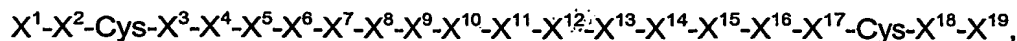
From figures 7 and 8 it can be seen that when pHBP 20-44 was acetylated and amidated at the N- and C-terminal amino acids, respectively, the variant peptide became more inhibitory to the LPS and PGN induced IL-6 production compared to the unsubstituted peptide.

In order to identify essential amino acid residues in human and porcine HBP 20-44 involved in the effects observed (see figures 1 – 4), several variants with amino acid substitutions in defined positions were tested. From figure 6 it appears that the substitution of arginine to glutamine in position 34 of pHBP 20-44 completely abolished the inhibitory effect of the peptide in the presence of PGN.

From figures 7 and 8 it appears that when the N-terminal amino acid residue of the pHBP 20-44 was substituted with the human N-terminal amino acid residue, the variant became less inhibitory compared to the original porcine peptide in the presence of both LPS and PGN. When both the N- and C-terminal amino acid residues of hHBP 20-44 was substituted with the corresponding porcine amino acid residues, the variant became nearly non-stimulating compared to the unsubstituted human peptide in the presence of LPS and in the presence of PGN the substituted peptide became inhibitory to the IL-6 production. From figures 7 and 8 it also appears that the same pattern was observed when the C-terminal amino acid residue in hHBP 20-44 was replaced with the porcine C-terminal amino acid residue, or when C-terminal amino acid residue in pHBP 20-44 was replaced with the human C-terminal amino acid residue.

Claims

1. A peptide having a sequence of at most 44 amino acid residues comprising a motif of the formula



wherein

X can be an amino acid sequence or a single amino acid residue selected either from Group 1 consisting of Ala, Gly, and Ser;

Group 2 consisting of Arg and Lys,

Group 3 consisting of His, Ile, Leu, Met, Phe, Pro, Thr, Val, Trp, and Tyr,

Group 4 consisting of Asn and Gln, or

Group 5 consisting of Ala, Asn, Arg, Gln, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, Val,

wherein

X¹ can be represented by a sequence consisting of 2-5 amino acid residues or an amino acid residue selected from Group 2;

X² is selected from Group 5 or Group 3;

X³, X¹⁵ and X⁴ are selected from Group 1;

X⁵ is Thr or selected from Group 1;

X⁶, X¹¹, X¹², X¹³ and X⁷ are selected from Group 3;

X⁸ and X¹⁷ are selected from Group 1, 3 or 4;

X⁹ is selected from Group 5, 1 or 3;

X¹⁰ is selected from Group 2, 3 or 4;

X¹⁴ is Ser or selected from Group 3;

X¹⁶ and X¹⁸ is selected from Group 1 or 3

X¹⁹ can be represented by a sequence consisting of 2-5 amino acid residues or a single amino acid residue selected from Group 5, 2, or 4,

with the proviso, that when X¹ includes Pro, then X¹⁹ is Gln.

2. The peptide according to claim 1, wherein X^1 is represented by an amino acid sequence selected from SEQ ID NOS: 607-612.

3. The peptide according to claim 1 or 2, wherein X^1 is Arg.

5 4. The peptide according to any of the claims 1-5, wherein X^2 is Phe.

5. The peptide according to any of the claims 1-6, wherein X^3 is Ala or Gly.

10 6. The peptide according to any of the claims 1-7, wherein X^4 is Gly.

7. The peptide according to any of the claims 1-8, wherein X^5 is Ala.

8. The peptide according to any of the claims 1-9, wherein X^6 is Leu.

15 9. The peptide according to any of the claims 1-10, wherein X^7 is Ile, Leu, Met or Val.

10. The peptide according to any of the claims 1-11, wherein X^8 is His or Val.

20 11. The peptide according to any of the claims 1-12, wherein X^9 is Ala, Phe or Pro.

12. The peptide according to any of the claims 1-13, wherein X^{10} is Arg.

25 13. The peptide according to any of the claims 1-14, wherein X^{11} is Phe or Pro.

14. The peptide according to any of the claims 1-15, wherein X^{12} is His or Val.

30 15. The peptide according to any of the claims 1-16, wherein X^{13} is Ile, Leu, Met or Val.

16. The peptide according to any of the claims 1-17, wherein X^{14} is Thr.

17. The peptide according to any of the claims 1-18, wherein X^{15} is Ala.

35 18. The peptide according to any of the claims 1-19, wherein X^{16} is Ala.

19. The peptide according to any of the claims 1-20, wherein X¹⁷ is Ser.

20. The peptide according to any of the claims 1-21, wherein X¹⁸ is Phe.

21. The peptide according to any of the claims 1-22, wherein X¹⁹ is a sequence identified as SEQ ID NO: 613

22. The peptide according to claims any of the claims 1-23, wherein X¹⁹ is Arg or Gln.

23. The peptide according to claim 3, wherein the N-terminal of the polypeptide chain is modified.

24. The peptide according to claim 4, wherein the N-terminal amino group is acetylated.

25. The peptide according to claim 24, wherein the C-terminal of the polypeptide chain is modified.

26. The peptide according to claim 25, wherein the C-terminal carboxy group is amidated.

27. The peptide according to any of the claims 1-26, wherein said peptide has the sequence KQGRHFCGGALIHARFVMTAASCFR (SEQ ID NO: 595).

28. The peptide according to any of the claims 1-26, wherein said peptide has the sequence KQGRPFCGGALIHARFVMTAASCFR (SEQ ID NO: 596).

29. The peptide according to any of the claims 1-26, wherein said peptide has the sequence KQGRHFCGGALIHPRFVMTAASCFR (SEQ ID NO: 597).

30. The peptide according to any of the claims 1-26, wherein said peptide has the sequence KQGRPFCGGALIHPRFVMTAASCFR (SEQ ID NO: 598).

31. The peptide according to any of the claims 1-26, wherein said peptide has the sequence RFCSAATLVFRPHVLAGACFPRGQK (SEQ ID NO: 599).
- 5 32. The peptide according to any of the claims 1-26, wherein said peptide has the sequence NQGRPFCAGALVHPRFVLTAASCFR (SEQ ID NO: 600).
33. The peptide according to any of the claims 1-26, wherein said peptide has the sequence KQGRPFCAGALVHPRFVLTAASCFQ (SEQ ID NO: 601).
- 10 34. The peptide according to any of the claims 1-26, wherein said peptide has the sequence NQGRPFCAGALVHPRFVLTAASCFQ (SEQ ID NO: 602).
35. The peptide according to any of the claims 1-26, wherein said peptide has the sequence KQGRPFCAGALVHPQFVLTAASCFR (SEQ ID NO: 603).
- 15 36. The peptide according to any of the claims 1-26, wherein said peptide has the sequence LRGGHFCGATLIAPNFVMSAAHCVA (SEQ ID NO: 604).
37. The peptide according to any of the claims 1-26, wherein said peptide has the sequence RRGGHFCGATLIARNFVMSAVHCVN (SEQ ID NO: 605).
- 20 38. The peptide according to any of the claims 1-26, wherein said peptide has the sequence RSREYRCGGTLVSQRYILTAASCAA (SEQ ID NO: 606).
- 25 39. The peptide according to any of the claims 1-26, wherein said peptide has the sequence NQGRHFCCGALIHARFVMTAASCFQ (SEQ ID NO: 594).
40. The peptide according to any of the claims 1-26, wherein said peptide has the sequence KQGRPFCAGALVHPRFVLTAASCFR (SEQ ID NO: 593).
- 30 41. The peptide according to claim 39 or 40, wherein the C-terminal carboxy group of said peptide is amidated and/or the N-terminal amino group is acetylated.

42. The peptide according to claim 1, wherein the motif comprises a sequence of the formula Cys-X₍₁₁₎-Ala-Ala-Ser-Cys, wherein X₍₁₁₎-represents a contiguous sequence of 11 amino acids.

5 43. The peptide according to claims 1, 2 or 42, wherein the sequence comprises one or more amino acid sequences are selected from SEQ ID NOS: 12-39.

44. The peptide according to claims 1-26 or 42 wherein the sequence comprises one or more amino acid sequences are selected from SEQ ID NOS: 233-253.

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45. The peptide according to claims 1-26 or 42 and 44, wherein the sequence comprises one or more amino acid sequences are selected from SEQ ID NOS: 233-253 and SEQ ID NO: 34.

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46. The peptide according to claims 1-26 or 42 and 44-45, wherein the sequence comprises one or more amino acid sequences are selected from SEQ ID NOS: 233-253 and SEQ ID NO: 21.

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47. The peptide according to claims 1-26 or 42 and 44-45, wherein the sequence comprises one or more amino acid sequences are selected from SEQ ID NOS: 233-253 and SEQ ID NO: 21 and SEQ ID NO: 34.

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48. The peptide according to claims 1-26 and 42, wherein the sequence comprises one or more amino acid sequences are selected from SEQ ID NOS: 395-421.

49. The peptide according to claims 1-26 and 42, wherein the one or more amino acid sequences are derived from the sequence of human heparin-binding protein (hHBP) set forth in SEQ ID NO: 1.

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50. The peptide according to claims 1-26 and 42, wherein the one or more amino acid sequences are derived from the sequence of porcine heparin-binding protein (pHBP) set forth in SEQ ID NO: 588.

51. The peptide according to claims 1-26 and 42, wherein the one or more amino acid sequences are derived from the sequence of human neutrophil elastase set forth in SEQ ID NO: 589.

5 52. The peptide according to claims 1-26 and 42 comprising one or more amino acid sequences set forth in SEQ ID NOS: 2-587.

53. The peptide according to any of the claims 1-52, wherein said peptide is capable of inhibiting the secretion of cytokine IL-6 from monocytes.

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54. The peptide according to any of the claims 1-52, wherein said peptide is capable of stimulating the secretion of cytokine IL-6 from monocytes.

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55. A process for the production of a peptide as defined in any of the claims 1-54, comprising the steps of

a) providing an expression vector containing a DNA sequence encoding one or more of the amino acid sequences as defined in the claims 1-54,

20

b) transforming host cells with the vector of step (a);

c) culturing the transformed cells of step (b);

d) purifying the expressed peptide.

25

56. The process according to claim 55, wherein the host cells are selected from the group comprising recombinant bacterial, yeast, insect or mammalian cells.

30

57. Use of one or more peptides as defined in any of the claims 1-54 for the manufacture of a medicament for the treatment of Gram negative bacterial infection.

35

58. Use of one or more peptides as defined in any of the claims 1-54 for the manufacture of a medicament for the treatment of Gram positive bacterial infection.

59. Use of one or more peptides as defined in any of the claims 1-54 for the manufacture of a medicament for the treatment of sepsis, severe sepsis, septic shock and disseminated intravascular coagulation.

5

60. Use of one or more peptides as defined in any of the claims 1-54 for the manufacture of a medicament for the treatment of meningitis.

61. The use according to claim 58, wherein meningitis is meningococcal meningitis.

10

62. Use of one or more peptides as defined in any of the claims 1-54 for the manufacture of a medicament for the treatment of pneumonia.

63. The use according to claim 60, wherein pneumonia is pneumococcal pneumonia.

15

64. Use of one or more peptides as defined in any of the claims 1-52 and 54 for the manufacture of a medicament for the stimulation of inflammatory response.

20

65. Use of one or more peptides as defined in any of the claims 1-53 for the manufacture of a medicament for the inhibition of inflammatory response.

66. Use of one or more peptides as defined in any of the claims 1-54 for the manufacture of a medicament for the prevention of cell apoptosis.

25

67. Use of a peptide comprising two or more sequences set forth in SEQ ID NOS: 20-36, wherein said sequences constitute a contiguous sequence derived from the sequence of human HBP set forth in SEQ ID NO:1 for the manufacture of a medicament for the treatment of individuals having suppressed immune system, cancer, auto-immune diseases and/or trauma.

30

68. The use according to claim 67, wherein the peptide is having the sequence identified in SEQ ID NO: 594, fragments, or variants thereof.

69. The use according to claim 68, wherein the peptide has the N-terminal amino group acetylated and/or C-terminal carboxy group amidated.

5 70. Use of a peptide comprising the sequence comprises one or more amino acid sequences are selected from SEQ ID NOS: 233-253 and SEQ ID NO: 21 and SEQ ID NO: 34, wherein said sequences constitute a contiguous sequence derived from the sequence of porcine HBP set forth in SEQ ID NO: 588 for the manufacture of a medicament for the treatment of individuals to suppress a sustained inflammatory response.

10 71. The use according to claim 70, wherein the peptide is having the sequence identified in SEQ ID NO: 593, fragments, or variants thereof.

15 72. The use according to claim 71, wherein the peptide has the N-terminal amino group acetylated and/or C-terminal carboxy group amidated.

73. A pharmaceutical composition comprising a peptide as defined in claims 1-54.

Table 1

HBP function	Mono-functional agonist	Mono-functional antagonist
Capillary leakage		Edema, SIRS
Chemotaxis	Wound healing, local infections	Re-perfusion injury, brain edema
Monocyte activation	Local and systemic infections, (tumors)	Inflammatory diseases, SIRS
Activation contact phase system	(Infection)	SIRS, post-operative bleeding, pain, (inflammation)
Anti-apoptosis	Degenerative diseases	(Tumors)
Endotoxin binding	Endotoxin removal from septic patients	

Potential applications for mono-functional peptides

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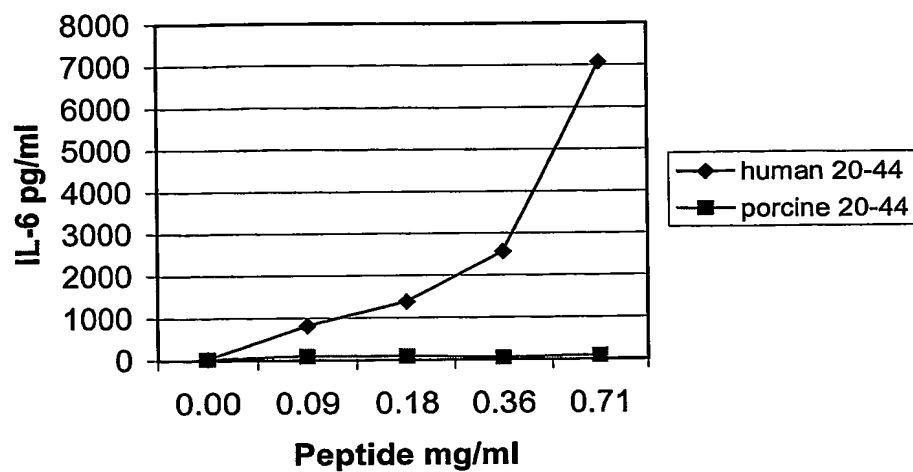
**Effect of 20-44 peptides in absence of
endotoxin**

Figure 1

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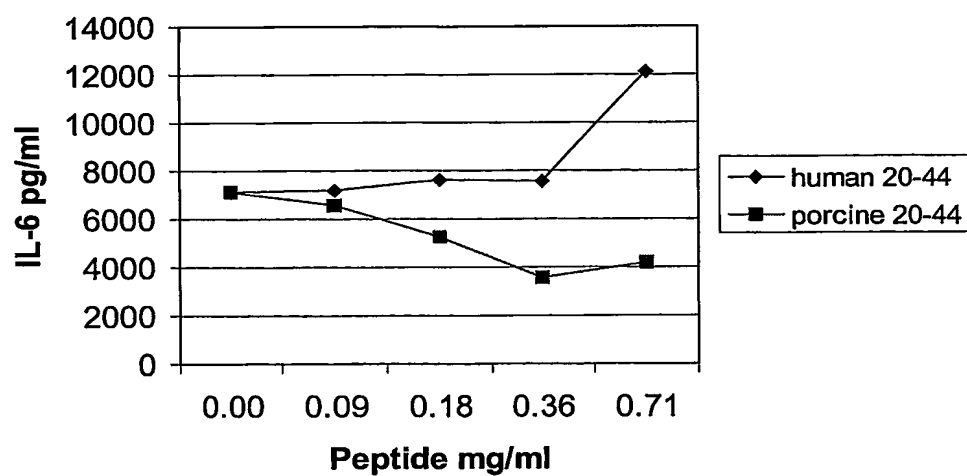
Effect of 20-44 peptides in presence of LPS

Figure 2

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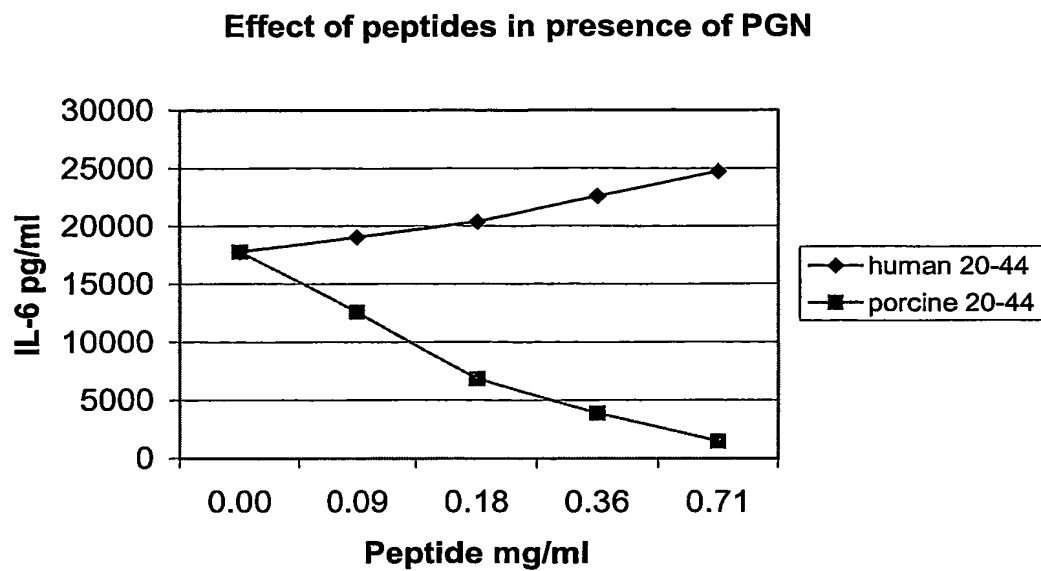


Figure 3

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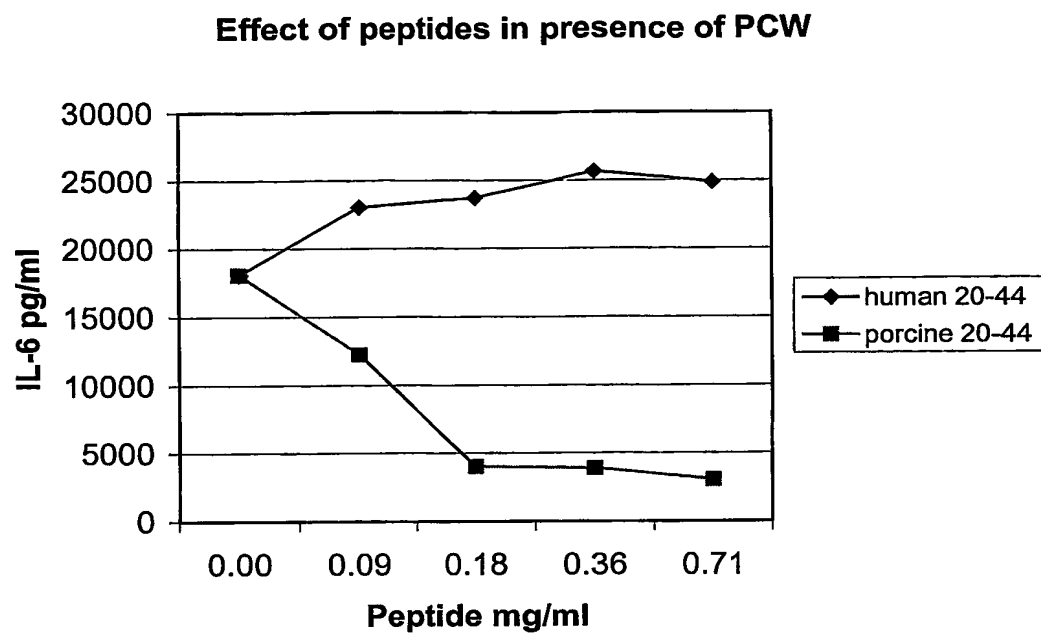


Figure 4

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**Effect of HBP 20-44 peptides
on LPS induced IL-6 secretion in the presence of PCW**

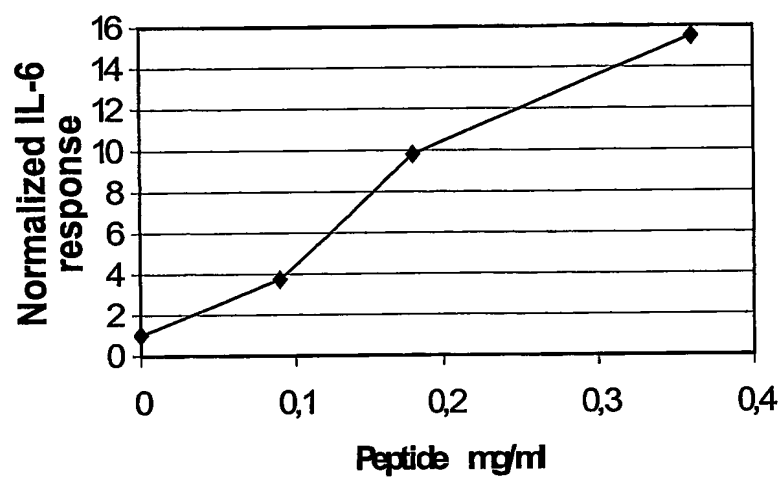


Figure 5

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Effect of N-Ac, C-amido hHBP 20-44 on PGN induced IL-6 secretion

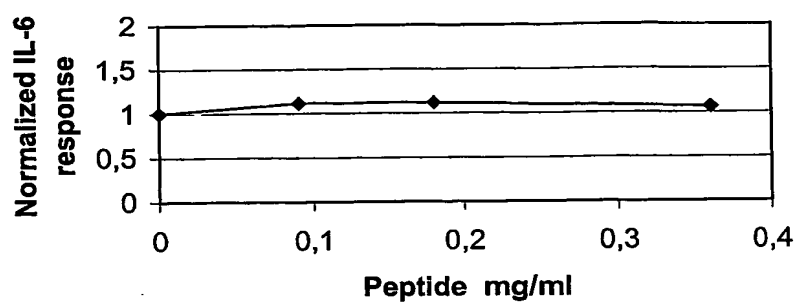


Figure 6

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**Effect of different substitutions in the sequence of hHBP and p HBP
on production of IL-6 induced by LPS.**

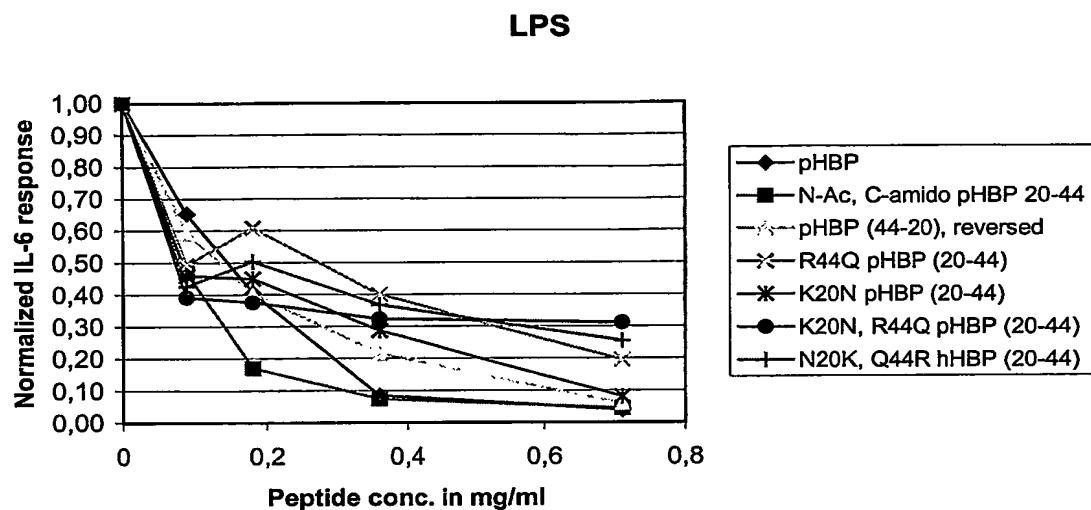


Figure 7

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**Effect of different substitutions in the sequence of hHBP and p HBP
on production of IL-6 induced by PGN**

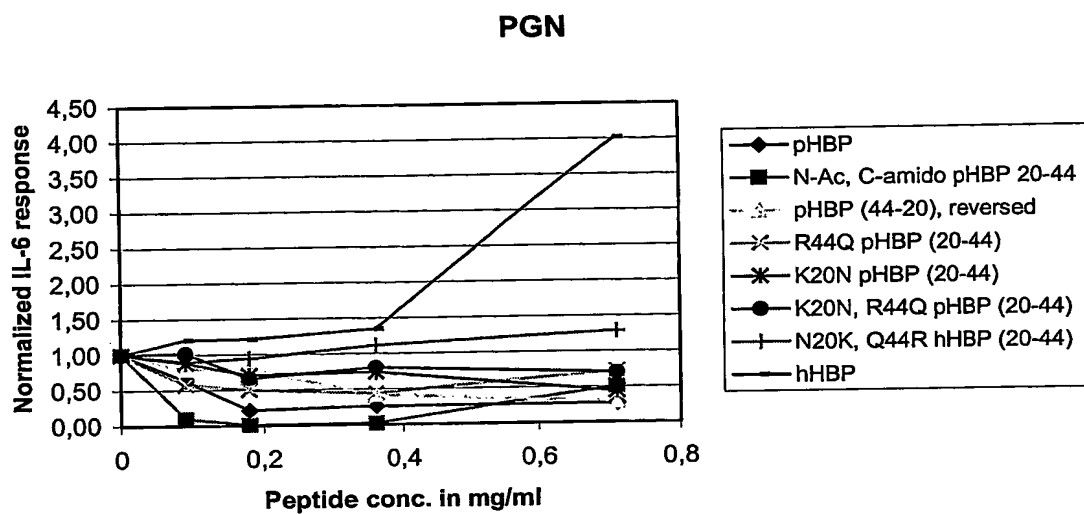


Figure 8

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<213> Homo sapiens

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35 40 45

Gly Val Ser Thr Val Val Leu Gly Ala Tyr Asp Leu Arg Arg Arg Glu
50 55 60

Arg Gln Ser Arg Gln Thr Phe Ser Ile Ser Ser Met Ser Glu Asn Gly
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Tyr Asp Pro Gln Gln Asn Leu Asn Asp Leu Met Leu Leu Gln Leu Asp
85 90 95

Arg Glu Ala Asn Leu Thr Ser Ser Val Thr Ile Leu Pro Leu Pro Leu
100 105 110

Gln Asn Ala Thr Val Glu Ala Gly Thr Arg Cys Gln Val Ala Gly Trp
115 120 125

Gly Ser Gln Arg Ser Gly Gly Arg Leu Ser Arg Phe Pro Arg Phe Val
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Asn Val Thr Val Thr Pro Glu Asp Gln Cys Arg Pro Asn Asn Val Cys
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Thr Gly Val Leu Thr Arg Arg Gly Gly Ile Cys Asn Gly Asp Gly Gly
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Thr Pro Leu Val Cys Glu Gly Leu Ala His Gly Val Ala Ser Phe Ser
180 185 190

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Arg Glu Ala Asn
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Glu Ala Asn Leu

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Ala Asn Leu Thr

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Asn Leu Thr Ser

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Leu Thr Ser Ser

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Thr Ser Ser Val

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Ser Ser Val Thr

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Ser Val Thr Ile

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Val Thr Ile Leu

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Pro Leu Pro Leu
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Leu Pro Leu Gln
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Thr Arg Cys Gln

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Trp Gly Ser Gln
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Gly Gly Arg Leu
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Gly Arg Leu Ser
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Arg Leu Ser Arg
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Arg Phe Pro Arg
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1

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Pro Arg Phe Val

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<400> 137

Arg Phe Val Asn

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<210> 138

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Phe Val Asn Val

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<210> 139

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Val Asn Val Thr
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Arg Pro Asn Asn
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Pro Asn Asn Val
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Asn Asn Val Cys

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Asn Val Cys Thr

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Val Cys Thr Gly

1

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Cys Thr Gly Val

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Thr Gly Val Leu

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Gly Val Leu Thr

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Val Leu Thr Arg

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Leu Thr Arg Arg

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Thr Arg Arg Gly
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Arg Arg Gly Gly
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Arg Gly Gly Ile
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Gly Gly Ile Cys
1

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Gly Ile Cys Asn
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Ile Cys Asn Gly
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Cys Asn Gly Asp
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Asn Gly Asp Gly
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Gly Asp Gly Gly
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<210> 169

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Asp Gly Gly Thr
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Gly Gly Thr Pro
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Gly Thr Pro Leu
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Thr Pro Leu Val
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Pro Leu Val Cys

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<210> 174

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<400> 174

Leu Val Cys Glu

1

<210> 175

<211> 4

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Val Cys Glu Gly

1

<210> 176

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Cys Glu Gly Leu

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<210> 177

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Glu Gly Leu Ala
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<210> 178

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Gly Leu Ala His
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Ala His Gly Val
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His Gly Val Ala

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Gly Val Ala Ser

1

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Val Ala Ser Phe

1

<210> 184

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Ala Ser Phe Ser

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<210> 185

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Ser Phe Ser Leu

1

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Phe Ser Leu Gly
1

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Ser Leu Gly Pro
1

<210> 188
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Leu Gly Pro Cys
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<210> 189
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Gly Pro Cys Gly
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Cys Gly Arg Gly
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Gly Arg Gly Pro
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Arg Gly Pro Asp
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Gly Pro Asp Phe

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<210> 195

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Pro Asp Phe Phe

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Asp Phe Phe Thr

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<210> 197

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<400> 197

Phe Phe Thr Arg

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<210> 198

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Phe Thr Arg Val
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Thr Arg Val Ala
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Arg Val Ala Leu
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Val Ala Leu Phe
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Ala Leu Phe Arg

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<400> 203

Leu Phe Arg Asp
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<210> 204
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<400> 204

Phe Arg Asp Trp
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<210> 205
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Arg Asp Trp Ile
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<210> 206
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Asp Trp Ile Asp
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Trp Ile Asp Gly
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Ile Asp Gly Val
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Asp Gly Val Leu
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Gly Val Leu Asn
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Val Leu Asn Asn
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Leu Asn Asn Pro
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Asn Asn Pro Gly
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Pro Gly Pro Gly

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Gly Pro Gly Pro

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Pro Gly Pro Ala

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Gly Gly Arg Lys

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Gly Arg Lys Ala

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Arg Lys Ala Arg

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Lys Ala Arg Pro

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Gly Gly Arg Arg

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Gln Pro Gln Glu
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Pro Gln Glu Phe
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Gln Glu Phe Pro
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Glu Phe Pro Phe
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Phe Pro Phe Leu
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Pro Phe Leu Ala

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Gln Gly Arg Pro

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Gly Arg Pro Phe

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Arg Pro Phe Cys

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Pro Phe Cys Ala

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Phe Cys Ala Gly

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Cys Ala Gly Ala

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Ala Gly Ala Leu

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Gly Ala Leu Val
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Ala Leu Val His
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Leu Val His Pro
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Val His Pro Arg
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His Pro Arg Phe
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Arg Phe Val Leu
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Phe Val Leu Thr
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Val Leu Thr Ala
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Leu Thr Ala Ala
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Cys Phe Arg Gly
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Arg Gly Lys Asn

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Gly Lys Asn Ser

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Lys Asn Ser Gly

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Asn Ser Gly Ser

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Ser Gly Ser Ala

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Gly Ser Ala Ser

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Ala Ser Val Val

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Asp Leu Arg Gln

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Leu Arg Gln Gln

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Arg Gln Gln Glu

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Gln Gln Glu Gln

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Gln Glu Gln Ser
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Glu Gln Ser Arg
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Ile Gln Lys Gln
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Phe Ser Ile Arg
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Ser Ile Arg Ser
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Ile Arg Ser Ile
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Arg Ser Ile Ser
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Ser Ile Ser Gln
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Ile Ser Gln Asn

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Ser Gln Asn Gly

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Gln Asn Gly Tyr

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Tyr Asp Pro Arg

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Asp Pro Arg Gln

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Pro Arg Gln Asn

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Arg Gln Asn Leu

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Leu Asn Asp Val

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Asn Asp Val Leu
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Asp Val Leu Leu
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Val Leu Leu Leu
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Glu Ala Arg Leu
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Ala Arg Leu Thr
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Thr Pro Ser Val
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Pro Ser Val Ala
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Ser Val Ala Leu
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Val Ala Leu Val
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Ala Leu Val Pro

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Leu Val Pro Leu

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Val Pro Leu Pro

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Pro Leu Pro Pro

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Leu Pro Pro Gln

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Pro Pro Gln Asn

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Pro Gln Asn Ala

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Ala Gly Thr Asn

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Gly Thr Asn Cys

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Thr Asn Cys Gln

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Asn Cys Gln Val

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Gly Trp Gly Thr

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Trp Gly Thr Gln

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Gly Thr Gln Arg
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Thr Gln Arg Leu
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Gln Arg Leu Arg
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Arg Leu Arg Arg
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Leu Arg Arg Leu
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Arg Arg Leu Phe
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Arg Leu Phe Ser
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Leu Phe Ser Arg
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Phe Ser Arg Phe

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<210> 317

<211> 4

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Phe Pro Arg Val

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Pro Arg Val Leu

1

<210> 319

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<400> 319

Arg Val Leu Asn

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Val Leu Asn Val

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<400> 321

Leu Asn Val Thr

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<400> 322

Thr Val Thr Ser

1

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<400> 323

Val Thr Ser Asn

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<400> 324

Thr Ser Asn Pro

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<400> 325

Ser Asn Pro Cys

1

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<400> 326

Asn Pro Cys Leu

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<400> 327

Pro Cys Leu Pro

1

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Cys Leu Pro Arg

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Leu Pro Arg Asp
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Pro Arg Asp Met
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Arg Asp Met Cys
1

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Asp Met Cys Ile
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Met Cys Ile Gly

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Cys Ile Gly Val

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<400> 335

Ile Gly Val Phe

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Gly Val Phe Ser

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Val Phe Ser Arg

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Phe Ser Arg Arg

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Ser Arg Arg Gly

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Arg Arg Gly Arg

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Arg Gly Arg Ile

1

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Gly Arg Ile Ser

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Arg Ile Ser Gln

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Ile Ser Gln Gly

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Gln Gly Asp Arg
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Leu Val Cys Asn
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Cys Asn Gly Leu
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Asn Gly Leu Ala
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Gly Leu Ala Gln

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Leu Ala Gln Gly

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Ala Gln Gly Val

1

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Gln Gly Val Ala

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<400> 358

Ala Ser Phe Leu

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<400> 359

Ser Phe Leu Arg

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Phe Leu Arg Arg

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<400> 361

Gln Lys Gln Gly

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<210> 362

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Phe Arg Arg Ser
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Arg Arg Ser Ser
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Arg Ser Ser Gly
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Ser Ser Gly Phe
1

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Ser Gly Phe Phe
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Gly Phe Phe Thr
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<210> 371

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Lys Gln Gly Arg
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<210> 372
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<400> 372

Leu Phe Arg Asn
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Phe Arg Asn Trp
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<400> 374

Arg Asn Trp Ile
1

<210> 375
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<400> 375

Asn Trp Ile Asp

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<211> 4

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<400> 376

Trp Ile Asp Ser

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<210> 377

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<400> 377

Ile Asp Ser Val

1

<210> 378

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<400> 378

Asp Ser Val Leu

1

<210> 379

<211> 4

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<400> 379

Ser Val Leu Asn
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Asn Asn Pro Pro
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Gly Gly Arg Arg
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<210> 382
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Gly Arg Arg Ala
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Arg Arg Ala Arg
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Arg Ala Arg Pro
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Ala Arg Pro His
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Arg Pro His Ala
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Pro His Ala Trp
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His Ala Trp Pro
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Ala Trp Pro Phe
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Trp Pro Phe Met
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Phe Met Val Ser
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Met Val Ser Leu
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<210> 394
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Val Ser Leu Gln
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Ser Leu Gln Leu
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Leu Gln Leu Arg

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Gln Leu Arg Gly

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Leu Arg Gly Gly

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Phe Cys Gly Ala
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Cys Gly Ala Thr
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Gly Ala Thr Leu

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Ala Thr Leu Ile

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Thr Leu Ile Ala

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Leu Ile Ala Pro

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Ile Ala Pro Asn

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Ala Pro Asn Phe
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Phe Val Met Ser
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Val Met Ser Ala
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Ala His Cys Val

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His Cys Val Ala

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Cys Val Ala Asn

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Val Ala Asn Val

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Ala Asn Val Asn

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Asn Val Asn Val

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Val Asn Val Arg

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Ala Val Arg Val

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Val Arg Val Val

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Arg Val Val Leu

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<210> 429

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Gly Ala His Asn
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Ala His Asn Leu
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His Asn Leu Ser
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Asn Leu Ser Arg
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Leu Ser Arg Arg
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Arg Glu Pro Thr
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Glu Pro Thr Arg

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Pro Thr Arg Gln

1

<210> 440

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Thr Arg Gln Val

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Gln Val Phe Ala
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<210> 443

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<223> Peptide fragment: amino acid residues 69-72 of hNLE

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<223> Peptide fragment: amino acid residues 70-73 of hNLE

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Phe Ala Val Gln
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<223> Peptide fragment: amino acid residues 71-74 of hNLE

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Ala Val Gln Arg
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<223> Peptide fragment: amino acid residues 72-75 of hNLE

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Val Gln Arg Ile

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Gln Arg Ile Phe
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Arg Ile Phe Glu
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Ile Phe Glu Asp
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Phe Glu Asp Gly
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<400> 451

Glu Asp Gly Tyr
1

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<400> 452

Asp Gly Tyr Asp
1

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Tyr Asp Pro Val
1

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Asp Pro Val Asn
1

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Pro Val Asn Leu

1

<210> 456

<211> 4

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Val Asn Leu Leu

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Asn Leu Leu Asn

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Leu Leu Asn Asp

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Asp Ile Val Ile
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Ile Val Ile Leu
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Val Ile Leu Gln

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Leu Gln Leu Asn

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Gln Leu Asn Gly

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Leu Asn Gly Ser

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Val Ala Leu Val

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Ala Leu Val Pro

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Val Pro Leu Pro

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Pro Leu Pro Ala

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Leu Pro Ala Gln

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Pro Ala Gln Gly

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Met Gly Trp Gly

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Trp Gly Leu Leu

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Asn Val Arg Ala

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Leu Leu Gly Arg

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Leu Gly Arg Asn

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Thr Val Val Thr

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Val Thr Ser Leu

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Thr Ser Leu Cys

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Cys Arg Arg Ser

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Arg Arg Ser Asn

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Arg Ser Asn Val

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Arg Ile Ser Gln

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Ile Ser Gln Gly

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Ser Gln Gly Asp

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Gln Gly Asp Ser

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Gly Asp Ser Gly

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Asp Ser Gly Thr

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Leu Val Cys Asn

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Cys Asn Gly Leu
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Leu Ile His Gly

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Ala Ser Phe Val
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Ser Phe Val Arg
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Arg Gly Gly Cys

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Gly Gly Cys Ala

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Gly Cys Ala Ser

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Cys Ala Ser Gly

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Ala Ser Gly Leu

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<210> 565

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Ser Gly Leu Tyr

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<210> 566

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<400> 566

Gly Leu Tyr Pro

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<210> 567

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Leu Tyr Pro Asp

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<210> 568

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Tyr Pro Asp Ala
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Pro Asp Ala Phe
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Asp Ala Phe Ala
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Ala Phe Ala Pro
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Ala Pro Val Ala
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Pro Val Ala Gln
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Val Ala Gln Phe
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Ala Gln Phe Val
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<223> Peptide fragment: amino acid residues 208-211 of hNLE

<400> 577

Gln Phe Val Asn
1

<210> 578
<211> 4
<212> PRT
<213> Artificial sequence

<220>
<223> Peptide fragment: amino acid residues 209-212 of hNLE

<400> 578

Phe Val Asn Trp
1

<210> 579
<211> 4
<212> PRT
<213> Artificial sequence

<220>
<223> Peptide fragment: amino acid residues 210-212 of hNLE

<400> 579

Val Asn Trp Ile
1

<210> 580
<211> 4
<212> PRT
<213> Artificial sequence

<220>
<223> Peptide fragment: amino acid residues 211-214 of hNLE

<400> 580

Asn Trp Ile Asp
1

<210> 581
<211> 4
<212> PRT
<213> Artificial sequence

<220>

<223> Peptide fragment: amino acid residues 212-215 of hNLE

<400> 581

Trp Ile Asp Ser

1

<210> 582

<211> 4

<212> PRT

<213> Artificial sequence

<220>

<223> Peptide fragment: amino acid residues 213-216 of hNLE

<400> 582

Ile Asp Ser Ile

1

<210> 583

<211> 4

<212> PRT

<213> Artificial sequence

<220>

<223> Peptide fragment: amino acid residues 214-217 of hNLE

<400> 583

Asp Ser Ile Ile

1

<210> 584

<211> 4

<212> PRT

<213> Artificial sequence

<220>

<223> Peptide fragment: amino acid residues 214-218 of hNLE

<400> 584

Ser Ile Ile Gln

1

<210> 585

<211> 4

<212> PRT

<213> Artificial sequence

<220>

<223> Peptide fragment: amino acid residues 43-46 of pHBP

<400> 585

Pro Arg Phe Val

1

<210> 586

<211> 4

<212> PRT

<213> Artificial sequence

<220>

<223> Peptide fragment: amino acid residues 190-194 of pHBP

<400> 586

Leu Arg Arg Arg

1

<210> 587

<211> 4

<212> PRT

<213> Artificial sequence

<220>

<223> Peptide fragment: amino acid residues 217-220 of pHBP

<400> 587

Asn Pro Pro Ala

1

<210> 588

<211> 221

<212> PRT

<213> Sus sp.

<400> 588

Ile Val Gly Gly Arg Arg Ala Gln Pro Gln Glu Phe Pro Phe Leu Ala
1 5 10 15

Ser Ile Gln Lys Gln Gly Arg Pro Phe Cys Ala Gly Ala Leu Val His
20 25 30

Pro Arg Phe Val Leu Thr Ala Ala Ser Cys Phe Arg Gly Lys Asn Ser
35 40 45

Gly Ser Ala Ser Val Val Leu Gly Ala Tyr Asp Leu Arg Gln Gln Glu
50 55 60

Gln Ser Arg Gln Thr Phe Ser Ile Arg Ser Ile Ser Gln Asn Gly Tyr

65

70

75

Asp Pro Arg Gln Asn Leu Asn Asp Val Leu Leu Leu Gln Leu Asp Arg
 85 90 95

Glu Ala Arg Leu Thr Pro Ser Val Ala Leu Val Pro Leu Pro Pro Gln
 100 105 110

Asn Ala Thr Val Glu Ala Gly Thr Asn Cys Gln Val Glu Ala Gly Trp
 115 120 125

Gly Thr Gln Arg Leu Arg Arg Leu Phe Ser Arg Phe Pro Arg Val Leu
 130 135 140

Asn Val Thr Val Thr Ser Asn Pro Cys Leu Pro Arg Asp Met Cys Ile
 145 150 155 160

Gly Val Phe Ser Arg Arg Gly Arg Ile Ser Gln Gly Asp Arg Gly Thr
 165 170 175

Pro Leu Val Cys Asn Gly Leu Ala Gln Gly Val Ala Ser Phe Leu Arg
 180 185 190

Arg Arg Phe Arg Arg Ser Ser Gly Phe Phe Thr Arg Val Ala Leu Phe
 195 200 205

Arg Asn Trp Ile Asp Ser Val Leu Asn Asn Pro Pro Ala
 210 215 220

<210> 589

<211> 267

<212> PRT

<213> Homo sapiens

<400> 589

Met Thr Leu Gly Arg Arg Leu Ala Cys Leu Phe Leu Ala Cys Val Leu
 1 5 10 15

Pro Ala Leu Leu Leu Gly Gly Thr Ala Leu Ala Ser Glu Ile Val Gly
 20 25 30

Gly Arg Arg Ala Arg Pro His Ala Trp Pro Phe Met Val Ser Leu Gln
 35 40 45

Leu Arg Gly Gly His Phe Cys Gly Ala Thr Leu Ile Ala Pro Asn Phe

50

55

60

Val Met Ser Ala Ala His Cys Val Ala Asn Val Asn Val Arg Ala Val
65 70 75 80

Arg Val Val Leu Gly Ala His Asn Leu Ser Arg Arg Glu Pro Thr Arg
85 90 95

Gln Val Phe Ala Val Gln Arg Ile Phe Glu Asn Gly Tyr Asp Pro Val
100 105 110

Asn Leu Leu Asn Asp Ile Val Ile Leu Gln Leu Asn Gly Ser Ala Thr
115 120 125

Ile Asn Ala Asn Val Gln Val Ala Gln Leu Pro Ala Gln Gly Arg Arg
130 135 140

Leu Gly Asn Gly Val Gln Cys Leu Ala Met Gly Trp Gly Leu Leu Gly
145 150 155 160

Arg Asn Arg Gly Ile Ala Ser Val Leu Gln Glu Leu Asn Val Thr Val
165 170 175

Val Thr Ser Leu Cys Arg Arg Ser Asn Val Cys Thr Leu Val Arg Gly
180 185 190

Arg Gln Ala Gly Val Cys Phe Gly Asp Ser Gly Ser Pro Leu Val Cys
195 200 205

Asn Gly Leu Ile His Gly Ile Ala Ser Phe Val Arg Gly Gly Cys Ala
210 215 220

Ser Gly Leu Tyr Pro Asp Ala Phe Ala Pro Val Ala Gln Phe Val Asn
225 230 235 240

Trp Ile Asp Ser Ile Ile Gln Arg Ser Glu Asp Asn Pro Cys Pro His
245 250 255

Pro Arg Asp Pro Asp Pro Ala Ser Arg Thr His
260 265

<210> 590

<211> 678

<212> DNA

<213> Homo sapiens

<400> 590
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agctgcttcc aaagccagaa ccccgggggtt agcacctggg tgctgggtgc ctatgacctg 180
aggcggcggg agaggcagtc ccgccagacg ttttccatca gcagcatgag cgagaatggc 240
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tgcgaggggc tggccacagg cgtggcctcc ttttccctgg ggccctgtgg ccgaggccct 600
gacttcttca cccgagtggc gctcttccga gactggatcg atggcgtttt aaacaatccg 660
ggaccggggc cagcctag 678

<210> 591
<211> 660
<212> DNA
<213> Sus sp.

<400> 591
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agctgcttcc gtggcaagaa cagcggaggt gcctctgtgg tgctgggggc ctatgacctg 180
aggcagcagg agcagtcccc gcagcattct ccatcaggag catcagccag aacggctatg 240
ayccccggca gaatctgaac gatgtgctgc tgctgcagct ggaccgtgag gccgactcac 300
ccccagtgtg gccctggtac cgctgcccc gcagaatgcc acagtggaag ctggcaccaa 360
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ttcagccgcc ggggccgcac cagccaggga gacagaggca cccccctcgt ctgcaacggc 540
ctggcgcagg gcgtggcctc cttcctccgg aggcgtttcc gcaggagctc cggcttcttc 600
accgcgctgg cgctcttcag aaattggatt gattcagttc tcaacaacc gccggcctga 660

<210> 592
<211> 750
<212> DNA

<213> Homo sapiens

<400> 592

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atgtccgcgg cacactgcgt agcaaagctt aacgttcgtg cggtgcggtg ggttctgggt      180
gtcataacc tgtctcgtcg agaaccgacc cgtcaagtgt tcgccgtgca gcgcattctc      240
gaaaacgggt acgaccgggt taacctgctg aacgacatcg tgattctgca actgaacgga      300
tccgccacca tcaacgcaa cgtgcaagtg gcacaactgc cagcccaagg tcgccgcctg      360
ggaaacggag tacaatgcct ggctatgggt tggggcctgc tcggccgtaa ccgtgggtatc      420
gctagcggtc tgcaagaact gaacgtgacc gtggttacct ccctgtgtcg acgctctaac      480
gtatgcactc tgggtgcgcg cgcgcaggct ggcgtttgtt tcggtgactc cggtagcccc      540
ctggtttgca acggtctgat ccatgggtatt gcctccttcg ttcgtgggtg ttgcgcctct      600
ggcctgtacc cggatgcatt tgccccgggtg gcacagtttg ttaactggat cgactctatc      660
attcagagat ccgaagacaa cccgtgtccg caccacgtg atccagatcc ggcctccaga      720
acacaccatc accatcacca ttaggaattc      750
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<210> 593

<211> 25

<212> PRT

<213> Artificial sequence

<220>

<223> Peptide fragment: amino acid residues 20-44 of pHBP

<400> 593

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Lys Gln Gly Arg Pro Phe Cys Ala Gly Ala Leu Val His Pro Arg Phe
1           5           10          15
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Val Leu Thr Ala Ala Ser Cys Phe Arg
20          25
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<210> 594

<211> 78

<212> PRT

<213> Artificial sequence

<220>

<223> Peptide fragment: amino acid residues 96-173 of pHBP

<400> 594

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Arg Glu Ala Arg Leu Thr Pro Ser Val Ala Leu Val Pro Leu Pro Pro
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<210>	597
<211>	25

<212> PRT
<213> Artificial sequence

<220>

<223> Peptide fragment: amino acid residues 20-44 of hHBP with mutations N20K,A33P,Q44R

<400> 597

Lys	Gln	Gly	Arg	His	Phe	Cys	Gly	Gly	Ala	Leu	Ile	His	Pro	Arg	Phe
1				5					10					15	

Val	Met	Thr	Ala	Ala	Ser	Cys	Phe	Arg
			20					25

<210> 598

<211> 25

<212> PRT

<213> Artificial sequence

<220>

<223> Peptide fragment: amino acid residues 20-44 of hHBP with mutations N20K,H24P,A33P,Q44R

<400> 598

Lys	Gln	Gly	Arg	Pro	Phe	Cys	Gly	Gly	Ala	Leu	Ile	His	Pro	Arg	Phe
1				5					10					15	

Val	Met	Thr	Ala	Ala	Ser	Cys	Phe	Arg
			20					25

<210> 599

<211> 25

<212> PRT

<213> Artificial sequence

<220>

<223> Reversed sequence: amino acid residues 20-44 of pHBP.

<400> 599

Arg	Phe	Cys	Ser	Ala	Ala	Thr	Leu	Val	Phe	Arg	Pro	His	Val	Leu	Ala
1				5					10					15	

Gly	Ala	Cys	Phe	Pro	Arg	Gly	Gln	Lys
			20					25

<210> 600

<211> 25

<212> PRT

<213> Artificial sequence

<220>

<223> Peptide fragment: amino acid residues 20-44 of pHBP with mutation K20N

<400> 600

Asn	Gln	Gly	Arg	Pro	Phe	Cys	Ala	Gly	Ala	Leu	Val	His	Pro	Arg	Phe
1				5					10					15	

Val	Leu	Thr	Ala	Ala	Ser	Cys	Phe	Arg
			20					25

<210> 601

<211> 25

<212> PRT

<213> Artificial sequence

<220>

<223> Peptide fragment: amino acid residues 20-44 of pHBP with mutation R44Q

<400> 601

Lys	Gln	Gly	Arg	Pro	Phe	Cys	Ala	Gly	Ala	Leu	Val	His	Pro	Arg	Phe
1				5					10					15	

Val	Leu	Thr	Ala	Ala	Ser	Cys	Phe	Gln
			20					25

<210> 602

<211> 25

<212> PRT

<213> Artificial sequence

<220>

<223> Peptide fragment: amino acid residues 20-44 of pHBP with mutations K20N,R44Q

<400> 602

Asn	Gln	Gly	Arg	Pro	Phe	Cys	Ala	Gly	Ala	Leu	Val	His	Pro	Arg	Phe
1				5					10					15	

Val	Leu	Thr	Ala	Ala	Ser	Cys	Phe	Gln
			20					25

<210> 603

<211> 25

<212> PRT

<213> Artificial sequence

<220>

<223> Peptide fragment: amino acid residues 20-44 of pHBP with

mutation R34Q

<400> 603

Lys Gln Gly Arg Pro Phe Cys Ala Gly Ala Leu Val His Pro Gln Phe
1 5 10 15

Val Leu Thr Ala Ala Ser Cys Phe Arg
20 25

<210> 604

<211> 25

<212> PRT

<213> Artificial sequence

<220>

<223> Peptide fragment consisting of amino acid residues 20-44 of human neutrophil elastase

<400> 604

Leu Arg Gly Gly His Phe Cys Gly Ala Thr Leu Ile Ala Pro Asn Phe
1 5 10 15

Val Met Ser Ala Ala His Cys Val Ala
20 25

<210> 605

<211> 25

<212> PRT

<213> Artificial sequence

<220>

<223> Peptide fragment consisting of amino acid residues 20-44 of murine neutrophil elastase

<400> 605

Arg Arg Gly Gly His Phe Cys Gly Ala Thr Leu Ile Ala Arg Asn Phe
1 5 10 15

Val Met Ser Ala Val His Cys Val Asn
20 25

<210> 606

<211> 25

<212> PRT

<213> Artificial sequence

<220>

<223> Peptide fragment: amino acid residues 20-44 of A. gambiae EAA01962

<400> 606

Arg Ser Arg Glu Tyr Arg Cys Gly Gly Thr Leu Val Ser Gln Arg Tyr
1 5 10 15

Ile Leu Thr Ala Ala Ser Cys Ala Ala
20 25

<210> 607

<211> 5

<212> PRT

<213> Artificial sequence

<220>

<223> R1 amino acid sequence (claim 2)

<400> 607

Lys Gln Gly Arg Pro
1 5

<210> 608

<211> 5

<212> PRT

<213> Artificial sequence

<220>

<223> R1 amino acid sequence (claim 2)

<400> 608

Lys Gln Gly Lys Pro
1 5

<210> 609

<211> 5

<212> PRT

<213> Artificial sequence

<220>

<223> R1 amino acid sequence (claim 2)

<400> 609

Arg Gln Gly Arg Pro
1 5

<210> 610

<211> 5

<212> PRT

<213> Artificial sequence

<220>

<223> R1 amino acid sequence (claim 2)

<400> 610

Arg Gln Gly Lys Pro
1 5

<210> 611

<211> 5

<212> PRT

<213> Artificial sequence

<220>

<223> R1 amino acid sequence (claim 2)

<400> 611

Asn Gln Gly Arg His
1 5

<210> 612

<211> 5

<212> PRT

<213> Artificial sequence

<220>

<223> R1 amino acid sequence (claim 2)

<400> 612

Asn Gln Gly Lys His
1 5

<210> 613

<211> 5

<212> PRT

<213> Artificial sequence

<220>

<223> R19 amino acid sequences (claim 21)

<400> 613

Pro Arg Gly Gln Lys
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